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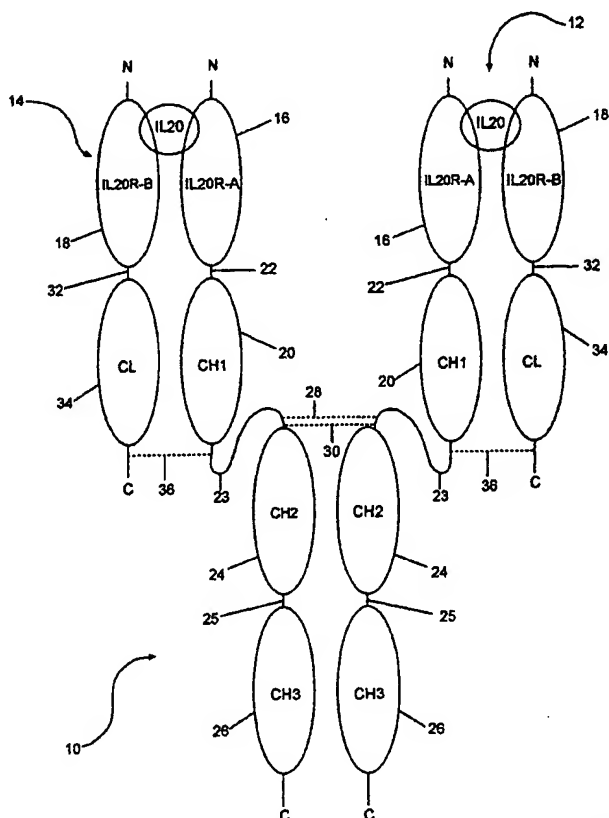
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[Continued on next page]

(54) Title: METHOD FOR TREATING INFLAMMATION



(57) Abstract: A method for treating IL-20 induced inflammation. An antagonist to IL-20 is administered to treat inflammation and associated diseases. The antagonist can be an antibody that binds to IL-20 or its receptor or a soluble receptor that binds to IL-20. Examples of such diseases are adult respiratory disease, psoriasis, eczema, contact dermatitis, atopic dermatitis, septic shock, multiple organ failure, inflammatory lung injury, bacterial pneumonia, inflammatory bowel disease, rheumatoid arthritis, asthma, ulcerative colitis and Crohn's disease.

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METHOD FOR TREATING INFLAMMATION

BACKGROUND OF THE INVENTION

The teachings of all of the references cited herein are incorporated in
10 their entirety herein by reference.

Inflammation normally is a localized, protective response to trauma or
microbial invasion that destroys, dilutes, or walls-off the injurious agent and the injured
tissue. It is characterized in the acute form by the classic signs of pain, heat, redness,
swelling, and loss of function. Microscopically, it involves a complex series of events,
15 including dilation of arterioles, capillaries, and venules, with increased permeability and
blood flow, exudation of fluids, including plasma proteins, and leukocyte migration into
the area of inflammation.

Diseases characterized by inflammation are significant causes of
morbidity and mortality in humans. Commonly, inflammation occurs as a defensive
20 response to invasion of the host by foreign, particularly microbial, material. Responses
to mechanical trauma, toxins, and neoplasia also may results in inflammatory reactions.
The accumulation and subsequent activation of leukocytes are central events in the
pathogenesis of most forms of inflammation. Deficiencies of inflammation compromise
the host. Excessive inflammation caused by abnormal recognition of host tissue as
25 foreign or prolongation of the inflammatory process may lead to inflammatory diseases
as diverse as diabetes, arteriosclerosis, cataracts, reperfusion injury, and cancer, to post-
infectious syndromes such as in infectious meningitis, rheumatic fever, and to
rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis. The
centrality of the inflammatory response in these varied disease processes makes its
30 regulation a major element in the prevention control or cure of human disease.

An important cytokine in the inflammatory process is interleukin-8 (IL-8). IL-8 is a chemokine. It was identified as an agonist for neutrophils on the basis of two effects, chemotaxis and the release of granule enzymes. IL-8 binds to two receptors on neutrophils. IL-8 receptors are also found on monocytes, basophils, and eosinophils.

5 In human fibroblasts, cytomegalovirus has been shown to induce the expression of IL-8 receptors and to replicate more rapidly when cells are exposed to IL-8. IL-8 is a potent chemoattractant for neutrophils; and the early stages of periodontal disease are characterized by the influx of neutrophils. IL-8 is a potent inducer of angiogenesis in several angiogenesis-dependent chronic inflammatory conditions, including rheumatoid

10 arthritis, psoriasis, and idiopathic pulmonary fibrosis. Additionally, IL-8 is an important source of angiogenic activity in human lung cancer. Also, IL-8 expression correlates with experimental metastatic activity of some melanoma cell lines. Thus, an effective method to treat inflammatory diseases would be to administer an agent that would inhibit IL-8.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIGURES: 1-8 are schematic representations of a representative number of embodiments of the IL-20 soluble receptor.

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DESCRIPTION OF THE INVENTION

The present invention fills this need by providing for a method for

25 treating inflammation in which IL-20 plays a role, comprising administering to a mammal in need of treatment of inflammation an antagonist to IL-20 or an antagonist to the IL-20 receptor. The antagonist to IL-20 can be an antibody, antibody fragment or single-chain antibody that binds to IL-20, a soluble receptor that binds to IL-20. The antagonist to the IL-20 receptor can be an antibody, antibody fragment, single-chain

30 antibody or small molecule that binds to the IL-20 receptor. Also an anti-sense nucleotide that binds to the mRNA that encodes IL-20 can be used as an antagonist. We have shown that IL-20 up-regulates IL-8. Inflammatory diseases in which IL-8 plays a

significant role, and for which a decrease in IL-8 would be beneficial are, adult respiratory disease (ARD), septic shock, multiple organ failure, inflammatory lung injury such as asthma or bronchitis, bacterial pneumonia, psoriasis and inflammatory bowel disease such as ulcerative colitis and Crohn's disease, eczema, atopic dermatitis and contact dermatitis. Thus, antagonists to IL-20 can be used to treat these diseases.

The teachings of all the references cited herein are incorporated in their entirety by reference.

Definitions

Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

The term "complement/anti-complement pair" denotes non-identical moieties that form a non-covalently associated, stable pair under appropriate conditions. For instance, biotin and avidin (or streptavidin) are prototypical members of a complement/anti-complement pair. Other exemplary complement/anti-complement pairs include receptor/ligand pairs, antibody/antigen (or hapten or epitope) pairs, sense/antisense polynucleotide pairs, and the like. Where subsequent dissociation of the complement/anti-complement pair is desirable, the complement/anti-complement pair preferably has a binding affinity of $<10^9 \text{ M}^{-1}$.

The term "complements of a polynucleotide molecule" is a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

The term "contig" denotes a polynucleotide that has a contiguous stretch of identical or complementary sequence to another polynucleotide. Contiguous sequences are said to "overlap" a given stretch of polynucleotide sequence either in their entirety or along a partial stretch of the polynucleotide. For example,
5 representative contigs to the polynucleotide sequence 5'-ATGGCTTAGCTT-3' are 5'-TAGCTTgagtct-3' and 3'-gtcgacTACCGA-5'.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons contain
10 different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription. Such additional segments
15 include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

The term "isolated", when applied to a polynucleotide, denotes that the
20 polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with
25 which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78 (1985)).

An "isolated" polypeptide or protein is a polypeptide or protein that is
30 found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide is substantially free of other

polypeptides, particularly other polypeptides of animal origin. It is preferred to provide the polypeptides in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide in alternative physical forms, such as dimers or
5 alternatively glycosylated or derivatized forms.

The term "operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, *e.g.*, transcription initiates in the promoter and proceeds through the coding segment to the terminator.

10 A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides
15 ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length
20 and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nucleotides in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10
25 amino acid residues are commonly referred to as "peptides".

The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

30 A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate

groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present
5 nonetheless.

The term "receptor" denotes a cell-associated protein that binds to a bioactive molecule (i.e., a ligand) and mediates the effect of the ligand on the cell. Membrane-bound receptors are characterized by a multi-domain structure comprising an extracellular ligand-binding domain and an intracellular effector domain that is
10 typically involved in signal transduction. Binding of ligand to receptor results in a conformational change in the receptor that causes an interaction between the effector domain and other molecule(s) in the cell. This interaction in turn leads to an alteration in the metabolism of the cell. Metabolic events that are linked to receptor-ligand interactions include gene transcription, phosphorylation, dephosphorylation, increases
15 in cyclic AMP production, mobilization of cellular calcium, mobilization of membrane lipids, cell adhesion, hydrolysis of inositol lipids and hydrolysis of phospholipids. In general, receptors can be membrane bound, cytosolic or nuclear, monomeric (*e.g.*, thyroid stimulating hormone receptor, beta-adrenergic receptor) or multimeric (*e.g.*, PDGF receptor, growth hormone receptor, IL-3 receptor, GM-CSF receptor, G-CSF
20 receptor, erythropoietin receptor and IL-6 receptor).

The term "secretory signal sequence" denotes a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the
25 secretory peptide during transit through the secretory pathway.

Molecular weights and lengths of polymers determined by imprecise analytical methods (*e.g.*, gel electrophoresis) will be understood to be approximate values. When such a value is expressed as "about" X or "approximately" X, the stated value of X will be understood to be accurate to $\pm 10\%$.

Introduction

The present invention relates to the treatment of inflammation and inflammatory diseases in which IL-20 plays a role either in initiating or spreading or maintenance by administering to the afflicted individual an antagonist to IL-20. That antagonist can be an antibody to IL-20, a soluble receptor that binds to IL-20, an anti-sense molecule or an antibody that binds to either the IL-20RA subunit or the IL-20RB subunit of the IL-20 receptor.

IL-20 is defined and methods for producing it and antibodies to IL-20 are contained in International Patent Application No. PCT/US98/25228, publication no. WO 99/27103, published November 25, 1998 and U.S. Patent Application No. 09/313,458 filed May 17, 1999. The polynucleotide and polypeptide of human IL-20 are represented by SEQ ID NOs: 1 - 4, and mouse IL-20 by SEQ ID NOs: 5-9.

The receptor to IL-20 has been discovered and is a heterodimer comprised of the polypeptide termed 'IL-20RA' (formally called Zcytor7) and a polypeptide termed 'IL-20RB'. The IL-20RA polypeptide, nucleic acid that encodes it, antibodies to IL-20RA, and methods for producing it are disclosed in U.S. Patent No. 5,945,511 issued August 31, 1999. SEQ ID NOs: 10 - 12 are the IL-20RA polynucleotides and polypeptides. The extracellular domain of the human IL-20RA is comprised of a polypeptide selected from the group consisting of SEQ ID NOs: 12, 55, 63 and 65, the full-length receptor subunit being comprised of SEQ ID NO: 11. The extracellular domain of mouse IL-20RA is SEQ ID NO: 38, SEQ ID NO: 37 being the entire mouse IL-20RA.

The extracellular domain of IL-20RB (SEQ ID NOs: 13-14, and a variant SEQ ID NOs: 18 and 19) is comprised of a polypeptide selected from the group consisting of SEQ ID NOs: 15, 59, 61, 67, 68 and 69. Preferably, the extracellular domain of the IL-20RA polypeptide and the extracellular domain of the IL-20RB polypeptide are covalently linked together. In a preferred embodiment one extracellular subunit polypeptide has a constant region of a heavy chain of an immunoglobulin fused to its carboxy terminus and the other extracellular subunit has a constant light chain of an immunoglobulin (Ig) fused to its carboxy terminus such that the two polypeptides come together to form a soluble receptor and a disulfide bond is formed between the heavy and the light Ig chains. In another method, a peptide linker could be fused to the two carboxy-termini of the polypeptides to form a covalently bonded soluble receptor.

SEQ ID NOs: 22 and 23 are constructs of the extracellular domain of IL-20RA fused to a mutated human immunoglobulin gamma 1 constant region produced according to the procedure set forth in example 5. SEQ ID NO: 62 is the predicted mature sequence without the signal sequence. SEQ ID NOs: 20 and 21 are constructs of the extracellular domain of IL-20RB fused to wild type human immunoglobulin kappa light chain constant region produced according to the procedure of example 5. SEQ ID NO: 60 is the predicted mature sequence without the signal sequence. Figure 1 depicts the heterotetramer produced by example 5.

SEQ ID NOs: 52 and 53 are constructs of the extracellular domain of IL-20RA fused to a mutated human immunoglobulin gamma 1 constant region produced according to the procedure set forth in example 12. SEQ ID NO: 54 is the predicted mature sequence without the signal sequence. SEQ ID NOs: 56 and 57 are constructs of the extracellular domain of IL-20RB fused to wild type human immunoglobulin kappa light chain constant region produced according to the procedure of example 12. SEQ ID NO: 58 is the predicted mature sequence without the signal sequence. The resultant heterotetramer is almost identical to that produced by example 5, the primary difference being the absence of a polypeptide linker between the extracellular domains and the beginning of the Ig constant regions, 22 in Figure 1. Hereinafter, the term "extracellular domain of a receptor" means the extracellular domain of the receptor or a portion of the extracellular domain that is necessary for binding to its ligand, in this case the ligand being IL-20.

One can link together the extracellular domains of IL-20RA and IL-20RB in a number of ways such that the resultant soluble receptor can bind to IL-20. Figures 1-8 illustrate a representative number of embodiments of the present invention. Common elements in each of the drawings are given the same number. Figure 1 represents the embodiment of the present invention produced according to example 5 below. The soluble receptor construct, designated 10, is comprised of two IL-20 binding site polypeptide chains designated 12 and 14. Each binding site is comprised of the extracellular domain of IL-20RA, designated 16, and the extracellular domain of IL-20RB designated 18.

The extracellular domain, 16, of IL-20RA is linked to the constant heavy one (CH1) domain, 20, of the human immunoglobulin gamma 1 heavy chain constant region via linker 22, which is SEQ ID NO:72. The CH1 domain, 20, is then linked to the CH2 domain, 24, via hinge region 23. The CH2 domain, 24, is linked to the CH3 domain, 26, via hinge region 25.

Comparing the construct of Figure 1 with SEQ ID NO:22, the extracellular domain, 16, of IL-20RA extends from amino acid residues 36, a valine, to

and including amino acid residue 249, a glutamine of SEQ ID NO:22. Polypeptide linker, 22, extends from amino acid residue 250, a glycine to and including amino acid residue 264, a serine, of SEQ ID NO:22. The CH1 domain, 22 of Figure 1, extends from amino acid residue 265, an alanine, to and including amino acid residue 362, a valine, of SEQ ID NO:22. Hinge region 23 of Figure 1 extends from amino acid residue 363, a glutamic acid to and including amino acid residue 377, a proline, of SEQ ID NO: 22. Chains 12 and 14 are disulfide-bonded together by means of disulfide bonds 28 and 30. The disulfide bonds are formed between the heavy chains by the cysteine residues at positions 373 and 376 of SEQ ID NO: 22 of each of the two heavy chains.

10 Extracellular domain, 18, of IL-20RB is linked to the constant region of the human kappa light chain (CL), 34 of Figure 1 via polypeptide linker 32, which is the polypeptide SEQ ID NO: 72. The extracellular domain, 18, of IL-20RB extends from amino acid residue 30, a valine, to and including amino acid residue 230, an alanine, of SEQ ID NO: 20. Polypeptide linker, 32, extends from amino acid residue 231, a glycine, to and including amino acid residue 245, a serine, of SEQ ID NO:20. The 15 kappa constant light region, 34, extends from amino acid residue 246, an arginine, to and including the final amino acid residue 352, a cysteine, of SEQ ID NO:20. The cysteine at position 352 of SEQ ID NO: 20 forms a disulfide bond, 36 in Figure 1, with the cysteine at position 367 of SEQ ID NO: 22. The constant light chain 34 is thus 20 linked to the hinge region, 23, by disulfide bond, 36. In this way, the extracellular domain, 16, of IL-20RA is linked to the extracellular domain, 18, of IL-20RB to form a soluble receptor.

If the cysteine residues at positions 373 and 376 of SEQ ID NO:22 were changed to different amino acid residues, the two IL-20 binding polypeptides, 12 and 25 14, would not be disulfide bonded together and would form a construct shown in Figure 2. having hinge region, 27.

Figure 3 shows a very simple soluble receptor 38 of the present invention wherein extracellular domain, 16, of IL-20RA is connected to the extracellular domain, 18, of IL-20RB by means of a polypeptide linker, 40. The 30 polypeptide linker extends from the amino terminus of extracellular domain, 16, of IL-20RA and is connected to the carboxyl terminus of the extracellular domain, 18, of IL-20RB. The polypeptide linker should be between 100-240 amino acids in length, preferably about 170 amino acid residues in length. A suitable linker would be comprised of glycine and serine residues. A possible linker would be multiple units of 35 SEQ ID NO: 72, preferably about 12.

Figure 4 shows an embodiment that has the extracellular domain, 16, of IL-20RA linked to the extracellular domain, 18, of IL-20RB by means of linker 40, as in Figure 3. While the extracellular domain, 16, of IL-20RA is linked to the CH1 domain, 20, as in Figure 1 by means of polypeptide linker 42, which should be about 30 amino acid residues in length. An ideal linker would be comprised of glycine and serine as in SEQ ID NO: 72, and the hinge sequence, 23 of Figure 1.

Figure 5 shows another possible embodiment of the present invention. In this embodiment, a polypeptide linker 44 of about 15 amino acid residue, *e.g.* SEQ ID NO: 72, links the carboxyl terminus of the extracellular domain, 18, of IL-20RB with the amino terminus of the extracellular domain, 16, of IL-20RA. A polypeptide linker 46 of about 30 amino acid residues extends from the carboxy terminus of the extracellular domain, 16, of IL-20RA to the CH2 domain. The carboxyl terminus of linker 46 would preferably be comprised of the hinge region extending from amino acid residue 363, a glutamic acid to and including amino acid residue 377, a proline, of SEQ ID NO: 22. Nonetheless, polypeptide linker 46 would ideally have at least one cysteine residue at its carboxyl terminus so a disulfide bond could be formed.

The soluble IL-20 receptor of Figure 6 is identical to that of Figure 1 except for the CH3 domain, 26 of Figure 1, is not present on the embodiment of Figure 6. The CH3 region begins at amino acid residue 488, a glycine, and extends to the last residue 594 of SEQ ID NO: 22.

Figure 7 shows a soluble IL-20 receptor construct that is identical to the construct of Figure 1 except both the CH2, and CH3 domains are absent. The CH2 and CH3 domains run from amino acid residue 378, an alanine, to the end of the polypeptide sequence of SEQ ID NO: 22.

Figure 8 shows a construct wherein both IL-20RA, 16, and IL-20RB have a polypeptide linker, 48, fused to their respective carboxyl termini. Each polypeptide linker has two cysteine residues such that when they are expressed the cysteines form two disulfide bonds, 50 and 52. In this case the polypeptide linker is comprised of the hinge region, 23 in Figure 1. The hinge region is comprised of amino acid residues 363, a glutamine, to and including amino acid residue 377 of SEQ ID NO: 22.

In another aspect of the invention, a method is provided for producing a soluble receptor comprised of extracellular domains of IL-20RA and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised of a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame the DNA that encodes the extracellular portion of IL-20RA and the DNA that encodes an immunoglobulin light chain constant

region;(b) introducing into the host cell a second DNA construct comprised of a transcriptional promoter operatively linked to a second secretory signal followed downstream by and in proper reading frame a DNA sequence that encodes the extracellular portion of IL-20RB and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3 and C_H4; (c) growing the host cell in an appropriate growth medium under physiological conditions to allow the secretion of a fusion protein comprised of the extracellular domain of IL-20RA and IL-20RB; and (d) isolating the polypeptide from the host cell. In one embodiment, the second DNA sequence further encodes an immunoglobulin heavy chain hinge region wherein the hinge region is joined to the heavy chain constant region domain. In another embodiment, the second DNA sequence further encodes an immunoglobulin variable region joined upstream of and in proper reading frame with the immunoglobulin heavy chain constant region.

In an alternative embodiment, a method is provided for producing a soluble receptor comprised of the extracellular domains of IL-20RA and IL-20RB comprising (a) introducing into a host cell a first DNA sequence comprised of a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame the DNA that encodes the extracellular portion of IL-20RB and the DNA that encodes an immunoglobulin light chain constant region;(b) introducing into the host cell a second DNA construct comprised of a transcriptional promoter operatively linked to a second secretory signal followed downstream by and in proper reading frame a DNA sequence that encodes the extracellular portion of IL-20RA and a DNA sequence that encodes an immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3 and C_H4; (c) growing the host cell in an appropriate growth medium under physiological conditions to allow the secretion of a dimerized heterodimeric fusion protein comprised of the extracellular domain of IL-20RA and IL-20RB; and (d) isolating the dimerized polypeptide from the host cell. In one embodiment, the second DNA sequence further encodes an immunoglobulin heavy chain hinge region wherein the hinge region is joined to the heavy chain constant region domain. In another embodiment, the second DNA sequence further encodes an immunoglobulin variable region joined upstream of and in proper reading frame with the immunoglobulin heavy chain constant region. (See U.S. Patent No. 5,843,725.)

As used herein, the term "antibodies" includes polyclonal antibodies, affinity-purified polyclonal antibodies, monoclonal antibodies, and antigen-binding fragments, such as F(ab')₂ and Fab proteolytic fragments. Genetically engineered intact antibodies or fragments, such as chimeric antibodies, Fv fragments, single chain

antibodies and the like, as well as synthetic antigen-binding peptides and polypeptides, are also included. Non-human antibodies may be humanized by grafting non-human CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. The binding affinity of an antibody can be readily determined by one of ordinary skill in the art, for example, by Scatchard analysis. A variety of assays known to those skilled in the art can be utilized to detect antibodies that bind to protein or peptide. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.) (Cold Spring Harbor Laboratory Press, 1988). Representative examples of such assays include: concurrent immunoelectrophoresis, radioimmunoassay, radioimmuno-precipitation, enzyme-linked immunosorbent assay (ELISA), dot blot or Western blot assay, inhibition or competition assay, and sandwich assay.

We have shown that IL-20 up-regulates IL-8. Inflammatory diseases in which IL-8 plays a significant role, and for which a decrease in IL-8 would be beneficial are, adult respiratory disease (ARD), septic shock, multiple organ failure, inflammatory lung injury such as asthma or bronchitis, bacterial pneumonia, psoriasis and inflammatory bowel disease such as ulcerative colitis and Crohn's disease, eczema, atopic dermatitis and contact dermatitis. Thus, antagonists to IL-20 can be used to treat these diseases.

Biology of IL-20, Its receptor and Its Role in Psoriasis

Two orphan class II cytokine receptors, both of which are expressed in skin, were identified as IL-20 receptor subunits. Both IL-20 receptor subunits are required for ligand binding, distinguishing their role from that of subunits in the four other known class II cytokine receptors. IL-20RA and IL-20RB are also coexpressed in a number of human tissues besides skin, including ovary, adrenal gland, testis, salivary gland, muscle, lung, kidney, heart and to a lesser degree the small intestine suggesting additional target tissues for IL-20 action. Additionally, we have detected IL-20RA mRNA but not IL-20RB mRNA in several human tissues including stomach, thyroid, pancreas, uterus, brain and prostate suggesting that IL-20RA may partner with other class II receptor subunits. We conclude that the IL-20 heterodimeric receptor is

structurally similar to other class II cytokine receptors and is expressed in skin where we have demonstrated activity of the IL-20 ligand.

Two lines of evidence indicate that a role IL-20 and its receptor are involved in psoriasis. This multigenic skin disease is characterized by increased
5 keratinocyte proliferation, altered keratinocyte differentiation, and infiltration of immune cells into the skin. The first line of evidence for a role of IL-20 in psoriasis is that the observed hyperkeratosis and thickened epidermis in the transgenic mice that resemble human psoriatic abnormalities. Decreased numbers of tonofilaments, thought to be related to defective keratinization, are a striking feature of human psoriasis.
10 Intramitochondrial inclusions have been found in both chemically induced and naturally occurring hyperplastic skin conditions in mice. The cause of the inclusions and their effects on mitochondrial function, if any, are unknown. We conclude that IL-20 transgenic mice exhibit many of the characteristics observed in human psoriasis.

A second line of evidence that implicates the IL-20 receptor in psoriasis
15 is that both IL-20RA and IL-20RB mRNA are markedly upregulated in human psoriatic skin compared to normal skin. Both IL-20 receptor subunits are expressed in keratinocytes throughout the epidermis and are also expressed in a subset of immune and endothelial cells. We propose that increased expression of an activated IL-20 receptor may alter the interactions between endothelial cells, immune cells and
20 keratinocytes, leading to dysregulation of keratinocyte proliferation and differentiation.

A crucial step in understanding the function of a novel cytokine is the identification and characterization of its cognate receptor. We have successfully used a structure-based approach to isolate a novel interleukin that ultimately led to the isolation of its receptor. IL-20 stimulates signal transduction in the human keratinocyte
25 HaCaT cell line, supporting a direct action of this novel ligand in skin. In addition, IL-1 β , EGF and TNF- α , proteins known to be active in keratinocytes and to be involved with proliferative and pro-inflammatory signals in skin, enhance the response to IL-20. In both HaCaT and BHK cells expressing the IL-20 receptor, IL-20 signals through STAT3.
30

Use of Antagonist to IL-20 to Treat Psoriasis

As indicated in the discussion above and the examples below, IL-20 is involved in the pathology of psoriasis. The present invention is in particular a method for treating psoriasis by administering antagonists to IL-20. The antagonists to IL-20
35 can either be a soluble receptor that binds to IL-20 or antibodies, single chain antibodies

or fragments of antibodies that bind to either IL-20 or the IL-20 receptor. The antagonists will thus prevent activation of the IL-20 receptor.

Psoriasis is one of the most common dermatologic diseases, affecting up to 1 to 2 percent of the world's population. It is a chronic inflammatory skin disorder characterized by erythematous, sharply demarcated papules and rounded plaques, covered by silvery micaceous scale. The skin lesions of psoriasis are variably pruritic. Traumatized areas often develop lesions of psoriasis. Additionally, other external factors may exacerbate psoriasis including infections, stress, and medications, *e.g.* lithium, beta blockers, and anti-malarials.

The most common variety of psoriasis is called plaque type. Patients with plaque-type psoriasis will have stable, slowly growing plaques, which remain basically unchanged for long periods of time. The most common areas for plaque psoriasis to occur are the elbows knees, gluteal cleft, and the scalp. Involvement tends to be symmetrical. Inverse psoriasis affects the intertriginous regions including the axilla, groin, submammary region, and navel, and it also tends to affect the scalp, palms, and soles. The individual lesions are sharply demarcated plaques but may be moist due to their location. Plaque-type psoriasis generally develops slowly and runs an indolent course. It rarely spontaneously remits.

Eruptive psoriasis (guttate psoriasis) is most common in children and young adults. It develops acutely in individuals without psoriasis or in those with chronic plaque psoriasis. Patients present with many small erythematous, scaling papules, frequently after upper respiratory tract infection with beta-hemolytic streptococci. Patients with psoriasis may also develop pustular lesions. These may be localized to the palms and soles or may be generalized and associated with fever, malaise, diarrhea, and arthralgias..

About half of all patients with psoriasis have fingernail involvement, appearing as punctate pitting, nail thickening or subungual hyperkeratosis. About 5 to 10 percent of patients with psoriasis have associated joint complaints, and these are most often found in patients with fingernail involvement. Although some have the coincident occurrence of classic rheumatoid arthritis, many have joint disease that falls into one of five type

associated with psoriasis: (1) disease limited to a single or a few small joints (70 percent of cases); (2) a seronegative rheumatoid arthritis-like disease; (3) involvement of the distal interphalangeal joints; (4) severe destructive arthritis with the development of "arthritis mutilans"; and (5) disease limited to the spine.

5 Psoriasis can be treated by administering antagonists to IL-20. The preferred antagonists are either a soluble receptor to IL-20 or antibodies, antibody fragments or single chain antibodies that bind to either the IL-20 receptor or to IL-20. The antagonists to IL-20 can be administered alone or in combination with other established therapies such as lubricants, keratolytics, topical corticosteroids, topical
10 vitamin D derivatives, anthralin, systemic antimetabolites such as methotrexate, psoralen-ultraviolet-light therapy (PUVA), etretinate, isotretinoin, cyclosporine, and the topical vitamin D3 derivative calcipotriol. The antagonists, in particularly the soluble receptor or the antibodies that bind to IL-20 or the IL-20 receptor can be administered to individual subcutaneously, intravenously, or transdermally using a cream or
15 transdermal patch that contains the antagonist of IL-20. If administered subcutaneously, the antagonist can be injected into one or more psoriatic plaques. If administered transdermally, the antagonists can be administered directly on the plaques using a cream containing the antagonist to IL-20.

20 **Use of Antagonists to IL-20 to Treat Inflammatory Conditions of the Lung.**

 Antagonists to IL-20 can be administered to a person who has asthma, bronchitis or cystic fibrosis or other inflammatory lung disease to treat the disease. The antagonists can be administered by any suitable method including intravenous, subcutaneous, bronchial lavage, and the use of inhalant containing an antagonist to IL-
25 20.

Administration of Antagonists to IL-20

 The quantities of antagonists to IL-20 necessary for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medications administered. Thus, treatment
30 dosages should be titrated to optimize safety and efficacy. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in vivo* administration of

these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Methods for administration include oral, intravenous, peritoneal, intramuscular, transdermal or administration into the lung or trachea in spray form by means of a nebulizer or atomizer. Pharmaceutically acceptable carriers will include water, saline, buffers to name just a few. Dosage ranges would ordinarily be expected from 1µg to 1000µg per kilogram of body weight per day. A dosage for an average adult of the IL-20 soluble receptor would be about 25 mg given twice weekly as a subcutaneous injection. A dosage of an antibody that binds to IL-20 would be about 25 mg given twice weekly. A mixture of antibodies that bind to the IL-20RA and IL-20RB subunits would be about 25 mg given twice weekly for an adult. Injections could be given at the site of psoriatic lesions for the treatment of psoriasis. For subcutaneous or intravenous administration of the antagonist to IL-20, the antibody or soluble receptor can be in phosphate buffered saline. Also in skin diseases such as psoriasis, the antagonist to IL-20 can be administered via an ointment or transdermal patch. The doses may be higher or lower as can be determined by a medical doctor with ordinary skill in the art. For a complete discussion of drug formulations and dosage ranges see *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing Co., Easton, Penn., 1996), and *Goodman and Gilman's: The Pharmacological Bases of Therapeutics*, 9th Ed. (Pergamon Press 1996).

20

The invention is further illustrated by the following non-limiting examples.

Example 1

Up-regulation of IL-8 by IL-20

Methods:

5 Normal Human Epidermal neonatal keratinocytes (NHEK) (from Clonetics) at passage 2 were plated and grown to confluency in 12 well tissue culture plates. KGM (Keratinocyte growth media) was purchased from Clonetics. When cells reached confluency, they were washed with KGM media minus growth factors = KBM (keratinocyte basal media). Cells were serum starved in KBM for 72 hours prior to the
10 addition of test compounds. Thrombin at 1 I.U./mL and trypsin at 25nM were used as positive controls. One mL of media/well was added. KBM only was used as the negative control.

 IL-20 was made up in KBM media and added at varying concentrations, from 2.5µg/ml down to 618ng/mL in a first experiment and from 2.5µg/mL down to
15 3ng/mL in a second experiment.

 Cells were incubated at 37° C, 5% CO₂ for 48 hours. Supernatants were removed and frozen at -80° C for several days prior to assaying for IL-8 and GM-CSF levels. Human IL-8 Immunoassay kit # D8050 (RandD Systems, Inc.) and human GM-CSF Immunoassay kit # HSGMO (RandD Systems, Inc.) were used to determine
20 cytokine production following manufacturer's instructions.

Results

 The results indicated that the expression of IL-8 and GM-CSF were induced by IL-20.

25

Example 2

Cloning of IL-20RB

Cloning of IL-20RB coding region

5

Two PCR primers were designed based on the sequence from *International Patent Application No. PCT/US99/03735* (publication no. WO 99/46379) filed on March 8, 1999. SEQ ID NO: 16 contains the ATG (Met1) codon with an *EcoRI* restriction site, SEQ ID NO: 17 contains the stop codon (TAG) with an *XhoI* restriction site. The PCR amplification was carried out using a human keratinocyte (HaCaT) cDNA library DNA as a template and SEQ ID NO: 16 and SEQ ID NO: 17 as primers. The PCR reaction was performed as follows: incubation at 94°C for 1 min followed by 30 cycles of 94°C for 30 sec and 68°C for 2 min, after additional 68°C for 4 min, the reaction was stored at 4°C. The PCR products were run on 1% Agarose gel, and a 1 kb DNA band was observed. The PCR products were cut from the gel and the DNA was purified using a QIAquick Gel Extraction Kit (Qiagen). The purified DNA was digested with *EcoRI* and *XhoI*, and cloned into a pZP vector that was called pZP7N. A pZP plasmid is a mammalian expression vector containing an expression cassette having the mouse metallothionein-1 promoter, human tPA leader peptide, multiple restriction sites for insertion of coding sequences, a Glu-Glu tag, and a human growth hormone terminator. The plasmid also has an *E. coli* origin of replication, a mammalian selectable marker expression unit having an SV40 promoter, an enhancer and an origin of replication, as well as a DHFR gene, and the SV40 terminator. Several IL-20RB-pZP7N clones were sequenced. They all contain three non-conservative mutations compared with the sequence of IL-20RB in PCT/US99/03735: (sequence IL-20RB-pZP7N), 146 Pro (CCC) – Thr (ACC), 148 His (CAT) – Asp (GAT), and 171 Thr (ACG) – Arg (AGG).

To verify the three substitutions in IL-20RB-pZP7N clone, PCR amplification was carried out using three difference cDNA sources – fetal skin marathon cDNA, HaCaT cDNA library DNA, and prostate smooth muscle cDNA library DNA – as templates. The PCR products were gel purified and sequenced. The

30

sequence of each of the three PCR products was consistent with that of the IL-20RB-pZP7N clone. IL-20RB is SEQ ID NO: 13 and 14, and the mature extracellular domain is SEQ ID NO: 15.

5

Example 3

Binding of IL-20 to IL-20RB/ IL-20RA Heterodimer

A cell-based binding assay was used to verify IL-20 binds to IL-20RA-IL-20RB heterodimer.

10

Expression vectors containing known and orphan Class II cytokine receptors (including IL-20RA and IL-20RB) were transiently transfected into COS cells in various combinations, which were then assayed for their ability to bind biotin-labeled IL-20 protein. The results show IL-20RB- IL-20RA heterodimer is a receptor for IL-20.

15 The procedure used is described below.

The COS cell transfection was performed in a 12-well tissue culture plate as follows: 0.5 µg DNA was mixed with medium containing 5 µl lipofectamine in 92 µl serum free Dulbecco's modified Eagle's medium (DMEM) (55 mg sodium pyruvate, 146 mg L-glutamine, 5 mg transferrin, 2.5 mg insulin, 1 µg selenium and 5 mg fetuin in 500 ml DMEM), incubated at room temperature for 30 minutes and then added to 400 µl serum free DMEM media. This 500 µl mixture was then added to 1.5 x 10⁵ COS cells/well and incubated for 5 hours at 37° C. 500 µl 20% fetal bovine serum (FBS) DMEM media was added and incubated overnight.

The assay, a modification of the "secretion trap" (Davis, S., *et al.*, *Cell* 25 87: 1161-1169 (1996), was performed as follows: cells were rinsed with PBS/1% bovine serum albumin (BSA) and blocked for 1 hour with TNB (0.1 M Tris-HCl, 0.15 M NaCl and 0.5% Blocking Reagent (NEN Renaissance TSA-Direct Kit Cat# NEL701) in water). This was followed by a one-hour incubation with 3 µg/ml biotinylated IL-20 protein in TNB. Cells were washed with PBS/1% BSA and incubated for another hour 30 with 1:300 diluted streptavidin-HRP (NEN kit) in TNB. Following another wash, cells were fixed for 15 minutes with 1.8% Formaldehyde in phosphate-buffered saline (PBS).

Cells were then washed with TNT (0.1 M Tris-HCL, 0.15 M NaCl, and 0.05% Tween-20 in water). Positive binding signals were detected following a five-minute incubation with fluorescein tyramide reagent diluted 1:50 in dilution buffer (NEN kit). Cells were washed with TNT, preserved with Vectashield Mounting Media (Vector Labs) diluted 1:5 in TNT, and visualized using an FITC filter on an inverted fluorescent microscope.

Example 4

Up-regulation of Inflammatory Cytokines by IL-20

Cell Treatment

The human keratinocyte cell line, HaCaT was grown at 37°C to several days post-confluence in T-75 tissue culture flasks. At this point, normal growth media (DMEM + 10% FBS) was removed and replaced with serum-free media. Cells were then incubated for two days at 37°C. DMEM was then removed and four flasks of cells per treatment were treated with one of each of the following conditions for four hours at 37°C: recombinant human (rh) IL-1 alpha at 5 ng/mL, rh IL-1 alpha at 20 ng/mL, rh IL-1 alpha at 5 ng/mL + IL-20 at 1µg/mL, IL-20 at 1µg/mL, or rh IL-10 at 10 ng/mL.

RNA Isolation

Following cytokine treatment, media was removed and cells were lysed using a guanidium thiocyanate solution. Total RNA was isolated from the cell lysate by an overnight spin on a cesium chloride gradient. The following day, the RNA pellet was resuspended in a TE/SDS solution and ethanol precipitated. RNA was then quantitated using a spectrophotometer, followed by a DNase treatment as per Section V.B. of Clontech's Atlas™ cDNA Expression Arrays User Manual (version PT3140-1/PR9X390, published 11/5/99). Quality of RNA samples was verified by purity calculations based on spec readings, and by visualization on agarose gel. Genomic contamination of the RNA samples was ruled out by PCR analysis of the beta-actin gene.

Probe Synthesis

Clontech's protocols for polyA+ enrichment, probe synthesis and hybridization to AtlasTM arrays were followed (see above, plus AtlasTM Pure Total RNA Labeling System User Manual, PT3231-1/PR96157, published 6/22/99). Briefly,

5 polyA+ RNA was isolated from 50 mg of total RNA using streptavidin coated magnetic beads (by Clontech, Paolo Alto, CA) and a magnetic particle separator. PolyA+ RNA was then labeled with $\alpha^{32}\text{P}$ -dATP via RT-PCR. Clontech CDS primers specific to the 268 genes on the AtlasTM human cytokine/receptor array (Cat. #7744-1) were used in the reaction. Labeled probe was isolated using column chromatography and counted

10 in scintillation fluid.

Array membrane Hybridization

AtlasTM arrays were pre-hybridized with Clontech ExpressHyb plus 100 mg/mL heat denatured salmon sperm DNA for at least thirty minutes at 68°C with

15 continuous agitation. Membranes were then hybridized with 1.9×10^6 CPM/mL (a total of 1.14×10^7 CPM) overnight at 68°C with continuous agitation. The following day, membranes were washed for thirty minutes x 4 in 2X SSC, 1% SDS at 68°C, plus for thirty minutes x 1 in 0.1X SSC, 0.5% SDS at 68°C, followed by one final room temperature wash for five minutes in 2X SSC. Array membranes were then placed in

20 Kodak plastic pouches sealed and exposed to a phosphor imager screen overnight at room temperature. The next day, phosphor screens were scanned on a phosphor imager and analyzed using Clontech's AtlasImageTM 1.0 software.

Results

25 Genes Up-regulated by IL-20

1. Tumor necrosis factor (TNF) was up-regulated 1.9-2.4 fold by IL-20.
2. Placental growth factors 1 & 2 (PLGF) were up-regulated 1.9-2.0 fold by IL-20.
3. Coagulating factor II receptor was up-regulated 2.0-2.5 fold by IL-20.
- 30 4. Calcitonin receptor was up-regulated 2.2-2.3 fold by IL-20.

5. TNF-inducible hyaluronate-binding protein TSG-6 was up-regulated 2.1-2.2 fold by IL-20.
6. Vascular endothelial growth factor (VEGF) receptor-1 precursor, tyrosine-protein kinase receptor (FLT-1) (SFLT) was up-regulated 2.1-2.7 fold by IL-20.
- 5 7. MRP-8 (calcium binding protein in macrophages MIF- related) was up-regulated 2.9-4.1 fold by IL-20.
8. MRP-14 (calcium binding protein in macrophages MIF-related) was up-regulated 3.0-3.8 fold by IL-20.
9. Relaxin H2 was up-regulated 3.14 fold by IL-20.
- 10 10. Transforming growth factor beta (TGF β) receptor III 300 kDa was up-regulated 2.4-3.6 fold by IL-20.

Genes Showing Synergy with IL-20 + IL-1 Treatment

1. Bone morphogenic protein 2a was up-regulated 1.8 fold with IL-20 treatment alone, 2.5 fold with IL-1 treatment alone, and 8.2 fold with both IL-20 and IL-1 treatment together.
- 15 2. MRP-8 was up-regulated 2.9 fold with IL-20 treatment alone, 10.7 fold with IL-1 treatment alone and 18.0 fold with both IL-20 and IL-1 treatment together.
3. Erythroid differentiation protein (EDF) was up-regulated 1.9 fold with IL-20 treatment alone, 9.7 fold with IL-1 treatment alone and 19.0 fold with both IL-20 and IL-1 treatment together.
- 20 4. MRP-14 (calcium binding protein in macrophages, MIF related) was up-regulated 3.0 fold with IL-20 treatment alone, 12.2 fold with IL-1 treatment alone and 20.3 fold with both IL-20 and IL-1 treatment together.
- 25 5. Heparin-binding EGF-like growth factor was up-regulated 2.0 fold with IL-20 treatment alone, 14 fold with IL-1 treatment alone and 25.0 fold with both IL-20 and IL-1 treatment together.
6. Beta-thromboglobulin-like protein was up-regulated 1.5 fold with IL-20 treatment alone, 15 fold with IL-1 treatment alone and 27 fold with both IL-20 and IL-1 treatment together.
- 30

7. Brain-derived neurotrophic factor (BDNF) was up-regulated 1.7 fold with IL-20 treatment alone, 25 fold with IL-1 treatment alone and 48 fold with both IL-20 and IL-1 treatment together.
8. Monocyte chemotactic and activating factor MCAF was up-regulated 1.3 fold with IL-20 treatment alone, 32 fold with IL-1 treatment alone and 56 fold with both IL-20 and IL-1 treatment together.

Example 5

IL-20RA/RB receptor-Ig fusion Heterotetramer

The expression vector pEZE3 was used to express the recombinant IL-20 receptor-Ig fusion protein. The plasmid pEZE3 is derived from pDC312. pDC312 was obtained through license from Immunex Corporation. The plasmids pDC312 and pEZE3 contain an EASE segment as described in WO 97/25420. The presence of the EASE segment in an expression vector can improve expression of recombinant proteins two to eight fold in stable cell pools.

The plasmid pEZE3 is a tricistronic expression vector that may be used to express up to three different proteins in mammalian cells, preferably Chinese Hamster Ovary (CHO) cells. The pEZE3 expression unit contains the cytomegalovirus (CMV) enhancer/promoter, the adenovirus tripartite leader sequence, a multiple cloning site for insertion of the coding region for the first recombinant protein, the poliovirus type 2 internal ribosome entry site, a second multiple cloning site for insertion of the coding region for the second recombinant protein, an encephalomyocarditis virus internal ribosome entry site, a coding segment for mouse dihydrofolate reductase, and the SV40 transcription terminator. In addition, pEZE3 contains an E. coli origin of replication and the bacterial beta lactamase gene.

The IL-20 receptor-Ig fusion protein is a disulfide linked heterotetramer consisting of two chains of the extracellular domain of the human IL-20RB fused to the wild type human immunoglobulin kappa light chain constant region and two chains of the human IL-20RA protein extracellular domain fused to a mutated human immunoglobulin gamma 1 constant region. The human immunoglobulin gamma 1

constant region contains amino acid substitutions to reduce FcγRI binding and C1q complement fixation.

The human IL-20RB extracellular domain human immunoglobulin kappa light chain constant region fusion construct was generated by overlap PCR. The
5 IL-20RB coding segment consists of amino acids 1 to 230. The template used for the PCR amplification of the IL-20R segment was generated IL-20RB human kappa light chain constant region expression construct as described below in Example 12. Oligonucleotide primers SEQ ID NO: 24 and SEQ ID NO: 25 were used to amplify the IL-20RB segment. The entire wild type human immunoglobulin kappa light chain
10 constant region was used. The template used for the PCR amplification of the wild type human immunoglobulin kappa light chain constant region segment was generated IL-20RB human kappa light chain constant region expression construct as described in Example 12. Oligonucleotide primers SEQ ID NO: 26 and SEQ ID NO: 27 were used to amplify the wild type human immunoglobulin kappa light chain constant region.
15 The two protein coding domains were linked by overlap PCR using oligonucleotides SEQ ID NO: 24 and SEQ ID NO: 27. A (Gly₄Ser)₃ (SEQ ID NO: 72) peptide linker was inserted between the two protein domains. The (Gly₄Ser)₃ peptide linker was encoded on the PCR primers SEQ ID NO: 26 and SEQ ID NO: 25. The resultant IL-20RB extracellular domain/kappa light chain constant region fusion construct is shown
20 by SEQ ID NOs: 20 and 21. The predicted mature polypeptide, minus the signal sequence, is SEQ ID NO: 60. The portion of the extracellular domain of IL-20RB that was actually used was comprised of the amino acid sequence of SEQ ID NO: 61. N-terminal sequencing resulted in the predicted amino acid sequence.

The human IL-20RA extracellular domain human immunoglobulin
25 gamma 1 heavy chain constant region fusion construct was generated by overlap PCR of four separate DNA fragments, each generated by separate PCR amplification reactions. The first fragment contained an optimized tPA (tissue plasminogen activator) signal sequence. The tPA signal sequence was amplified using oligonucleotide primers SEQ ID NO: 28 and SEQ ID NO: 29 using an in-house previously generated expression
30 vector as the template. The second fragment contained the IL-20RA extracellular domain-coding region consisting of amino acids 30 to 243 of SEQ ID NO: 11.

Oligonucleotide primers SEQ ID NO: 30 and SEQ ID NO: 31 were used to amplify this IL-20RA segment using a previously generated clone of IL-20RA as the template.

The human gamma 1 heavy chain constant region was generated from 2 segments. The first segment containing the C_H1 domain was amplified using
5 oligonucleotide primers SEQ ID NO: 32 and SEQ ID NO: 33 using a clone of the wild type human gamma 1 heavy chain constant region as the template. The second segment containing the remaining hinge, C_H2, and C_H3 domains of the human immunoglobulin gamma 1 heavy chain constant region was generated by PCR amplification using oligonucleotide primers SEQ ID NO: 34 and SEQ ID NO: 35. The template used for
10 this PCR amplification was from a previously generated human gamma 1 Fc construct that contained codons for amino acid substitutions to reduce FcγRI binding and C1q complement fixation as described in Example 12.

The four protein coding domains were linked by overlap PCR using oligonucleotides SEQ ID NO: 28 and SEQ ID NO: 35. A (Gly₄Ser)₃ peptide linker was
15 inserted between the IL-20RA and CH1 protein domains. The (Gly₄Ser)₃ peptide linker was encoded on the PCR primers SEQ ID NO: 32 and SEQ ID NO: 31. The IL-20RA extracellular domain/ domain human immunoglobulin gamma 1 heavy constant region fusion protein and DNA sequence are shown in SEQ ID NOs: 22 and 23. The predicted mature polypeptide sequence, minus the signal sequence, is SEQ ID NO: 62. The
20 portion of extracellular domain of IL-20RA that was actually used was comprised of SEQ ID NO: 63.

The IL-20RB extracellular domain human immunoglobulin kappa light chain constant region fusion coding segment was cloned into the second MCS while the human IL-20RA extracellular domain human immunoglobulin gamma 1 heavy chain
25 constant region fusion coding segment was cloned into the first MCS of pEZE3. The plasmid was used to transfect CHO cells. The cells were selected in medium without hypoxanthine or thymidine and the transgene was amplified using methotrexate. The presence of protein was assayed by Western blotting using anti human gamma 1 heavy chain constant region and anti human kappa light chain antibodies. N-terminal
30 sequencing revealed that the optimized tPA leader was not completely cleaved. The observed mass indicated that the first residue of the polypeptide sequence to be

pyroglutamic acid, and the N-terminal sequence appears to be pyroEEIHAELRRFRRVPCVSGG (SEQ ID NO: 64), the underlined portion being remnants of the tPA leader.

Example 6

5 IL-20 Transgenic Phenotype

Both human and mouse IL-20 were overexpressed in transgenic mice using a variety of promoters. The liver-specific mouse albumin promoter, directing expression of human IL-20, was used initially in an attempt to achieve circulating levels of protein. Subsequent studies were conducted using the keratin 14 (K14) promoter, 10 which primarily targets expression to the epidermis and other stratified squamous epithelia; the mouse metallothionein-1 promoter, which gives a broad expression pattern; and the E μ LCK promoter, which drives expression in cells of the lymphoid lineage. Similar results were obtained in all four cases, possibly because these promoters all give rise to circulating levels of IL-20.

15 In all cases, transgenic pups expressing the IL-20 transgene were smaller than non-transgenic littermates, had a shiny appearance with tight, wrinkled skin and died within the first few days after birth. Pups had milk in their stomachs indicating that they were able to suckle. These mice had swollen extremities, tail, nostril and mouth regions and had difficulty moving. In addition, the mice were frail, lacked 20 visible adipose tissue and had delayed ear and toe development. Low expression levels in liver (less than 100 mRNA molecules/cell) were sufficient for both the neonatal lethality and skin abnormalities. Transgenic mice without a visible phenotype either did not express the transgene, did not express it at detectable levels, or were mosaic.

Histologic analysis of the skin of the IL-20 transgenic mice showed a 25 thickened epidermis, hyperkeratosis and a compact stratum corneum compared to non-transgenic littermates. Serocellular crusts (scabs) were observed occasionally. Electron microscopic (EM) analysis of skin from transgenic mice showed intramitochondrial lipoid inclusions, mottled keratohyaline granules, and relatively few tonofilaments similar to that observed in human psoriatic skin and in mouse skin disease models. In 30 addition, many of the transgenic mice had apoptotic thymic lymphocytes. No other abnormalities were detected by histopathological analysis. These histological and EM

results support and extend the observed gross skin alterations.

Example 7

Specificity and Affinity of IL-20 for Its Receptor

5 The specificity and affinity of IL-20 for its receptor was determined using BHK cells stably transfected with IL-20RA, IL-20RB or both receptor subunits. Binding assays using radiolabeled ligand demonstrated that IL-20 bound to BHK transfectants expressing both IL-20RA and IL-20RB but not to untransfected cells nor to transfectants expressing either receptor subunit alone. Binding of ¹²⁵I-labeled IL-20
10 was eliminated in the presence of 100-fold excess of unlabeled IL-20 but not with 100-fold excess of the unrelated cytokine, IL-21. The binding affinity (K_D) of IL-20 to the IL-20RA/IL-20RB heterodimeric receptor was determined to be approximately 1.5 nM.

Example 8

15 IL-20 receptor Activation

To determine if IL-20 binding leads to receptor activation, the factor-dependent pre-B cell line BaF3 was co-transfected with IL-20RA and IL-20RB and treated with IL-20 at various concentrations. IL-20 stimulated proliferation in a dose-dependent manner and gave a detectable signal at 1.1 pM, with a half maximal response
20 at 3.4 pM. We note that the IL-20 concentration for the half maximal proliferative response in BaF3 cells is 1000X lower than that for half maximal binding affinity in BHK cells. Possible explanations for this large difference include the use of different cell lines, different receptor expression levels and different assay outputs. IL-20 also stimulated signal transduction in the biologically relevant human keratinocyte cell line
25 HaCaT, which naturally expresses IL-20RA and IL-20RB. Therefore, IL-20 binds and activates the heterodimeric IL-20RA/IL-20RB receptor at concentrations expected for a cytokine. While the negative controls containing untransfected BaF3

Example 9

Expression Analysis of IL-20RA and IL-20RB

RT-PCR analysis was performed on a variety of human tissues to determine the expression pattern of IL-20RA and IL-20RB. Both receptor subunits are most highly expressed in skin and testis. The significant result is that IL-20RA and IL-20RB are both expressed in skin, where they have been shown to mediate the IL-20-induced response. Both IL-20RA and IL-20RB are also both expressed in monocytes, lung, ovary, muscle, testis, adrenal gland, heart, salivary gland and placenta. IL-20RA is also in brain, kidney, liver, colon, small intestine, stomach, thyroid, pancreas, uterus and prostate while IL-20RB is not.

Example 10

IL-20RA and IL-20RB mRNA are Up-regulated in Psoriasis

In situ hybridization was used to determine whether IL-20 receptor expression is altered in psoriasis. Skin samples from four psoriasis patients and three unaffected patients were assayed with probes specific for the two-receptor subunit mRNAs. All four psoriatic skin samples had high levels of IL-20RA and IL-20RB mRNA in keratinocytes whereas normal skin samples did not have detectable levels of either receptor subunit mRNA. Positive signals in psoriatic skin were also observed in mononuclear immune cells and in endothelial cells in a subset of vessels. Therefore, both IL-20RA and IL-20RB are expressed in keratinocytes, immune cells and endothelial cells, the major cell types thought to interact in psoriasis.

Example 11

Cloning of Mouse IL-20RA

A cross-species hybridization probe was generated which contained the full-length cDNA fragment encoding human IL-20RA. A Southern blot of mouse genomic DNA and Northern blots of mouse RNA were performed to demonstrate that the human IL-20RA cDNA could specifically hybridize to mouse sequences. The Northern blot results indicated that mouse IL-20RA RNA was present in mouse embryo

day 15 and 17 as well as heart, brain, lung, liver, kidney, testes, spleen, thymus, liver, stomach, and small intestine.

The human IL-20RA full length DNA hybridization probe was used to screen a mouse genomic library. The library, which was obtained from Clontech (Palo Alto, CA), was generated from an MboI partial digest of mouse genomic DNA and cloned into the BamHI site of Lambda bacteriophage EMBL3 SP6/T7. Positive bacteriophage was plaque purified and bacteriophage DNA was prepared using Promega's Wizard Lambda Preps DNA Purification System. Two genomic restriction enzyme fragments, a 5.7 kb EcoRI fragment and an 8.0 kb SacI fragment, were generated from the positive bacteriophage and subcloned into pBluescript. DNA sequence analysis revealed the presence of 3 exons from the mouse ortholog to human IL-20RA.

PCR primers from the 5' UTR, SEQ ID NO: 40, and 3' UTR, SEQ ID NO: 41, were designed to generate a full-length mouse IL-20RA sequence by PCR amplification. Mouse embryo 15day plus 17 day cDNA was used as the template for the PCR amplification. PCR products were subcloned and sequenced for confirmation. The mouse sequences are SEQ ID NOs: 36 and 37. The mature extracellular domain is comprised of SEQ ID NO: 38.

Example 12

Construction of an IL-20 Receptor Heterotetramer

A vector expressing a secreted hIL-20RA/hIL-20B heterodimer was constructed. In this construct, the extracellular domain of hIL-20RA was fused to the heavy chain of IgG gamma 1 (IgGγ1), while the extracellular portion of IL-20RB was fused to human kappa light chain (human κ light chain).

Construction of IgG gamma 1 and human κ light fusion vectors

The heavy chain of IgGγ1 was cloned into the Zem229R mammalian expression vector (ATCC deposit No. 69447) such that any extracellular portion of a receptor having a 5' EcoRI and 3' NheI site can be cloned in, resulting in an N-terminal extracellular domain-C-terminal IgGγ1 fusion. The IgGγ1 fragment used in this construct was made by using PCR to isolate the IgGγ1 sequence from a Clontech

human fetal liver cDNA library as template. A PCR reaction using oligos SEQ ID NO: 42 and SEQ ID NO: 43 was run as follows: 40 cycles of 94° for 60 sec., 53°C for 60 sec., and 72° for 120 sec.; and 72°C for 7 minutes. PCR products were separated by agarose gel electrophoresis and purified using a QiaQuick™ (Qiagen Inc., Valencia, CA) gel extraction kit. The isolated, 990 bp, DNA fragment was digested with MluI and EcoRI (Boehringer-Mannheim), extracted with QiaQuick™ gel extraction kit and ligated with oligos SEQ ID NO: 44 and SEQ ID NO: 45, which comprise an MluI/EcoRI linker, into Zem229R previously digested with MluI and EcoRI using standard molecular biology techniques disclosed herein. This generic cloning vector was called Vector#76 hIgGgamma1 w/ Ch1 #786 Zem229R (Vector #76). The polynucleotide sequence of the extracellular domain of hIL-20RA fused to the heavy chain of IgG gamma 1 is shown in SEQ ID NO: 52 and the corresponding polypeptide sequence shown in SEQ ID NO: 53, the mature polypeptide, minus the signal sequence being comprised of SEQ ID NO: 54. The portion of the extracellular domain of IL-20RA used was comprised of SEQ ID NO: 55.

The human κ light chain was cloned in the Zem228R mammalian expression vector (ATCC deposit No. 69446) such that any extracellular portion of a receptor having a 5' EcoRI site and a 3' KpnI site can be cloned in, resulting in an N-terminal extracellular domain-C-terminal human κ light chain fusion. The human κ light chain fragment used in this construct was made by using PCR to isolate the human κ light chain sequence from the same Clontech hFetal Liver cDNA library used above. A PCR reaction was run using oligos SEQ ID NO: 46 and SEQ ID NO: 47. PCR products were separated by agarose gel electrophoresis and purified using a QiaQuick™ (Qiagen) gel extraction kit. The isolated, 315 bp, DNA fragment was digested with MluI and EcoRI (Boehringer-Mannheim), extracted with QiaQuick™ gel extraction kit and ligated with the MluI/EcoRI linker described above, into Zem228R previously digested with MluI and EcoRI using standard molecular biology techniques disclosed herein. This generic cloning vector was called Vector #77 h κ light #774 Zem228R (Vector #77). The polynucleotide sequence of the extracellular portion of IL-20RB fused to human kappa light chain is shown in SEQ ID NO: 56 and the corresponding polypeptide sequence shown in SEQ ID NO: 57, the mature polypeptide, minus the

signal sequence, is comprised of SEQ ID NO: 58. The portion of the extracellular domain of IL-20RB actually used was comprised of SEQ ID NO: 59.

Insertion of hIL-20RA and IL-20RB extracellular domains into fusion vector constructs

5 Using the construction vectors above, a construct having human IL-20RA fused to IgG γ 1 was made. This construction was done by using PCR to obtain human IL-20RA receptor from hIL-20RA /IgG Vector #102 with oligos SEQ ID NO: 48 and SEQ ID NO: 49 under conditions described as follows: 30 cycles of 94°C for 60 sec., 57°C for 60 sec., and 72°C for 120 sec.; and 72°C for 7 min. The resulting PCR
10 product was digested with EcoRI and NheI, gel purified, as described herein, and ligated into a previously EcoRI and NheI digested and band-purified Vector #76 (above). The resulting vector was sequenced to confirm that the human IL-20R α /IgG gamma 1 fusion (hIL-20RA /Ch1 IgG) was correct. The hIL-20RA /Ch1 IgG gamma 1 #1825 Zem229R vector was called vector #195. The IL-20RA/Ch1 IgG γ 1 sequence
15 thus obtained is depicted by SEQ ID NOs: 52 and 53. N-terminal sequencing indicated the presence of the predicted mature polypeptide sequence of SEQ ID NO: 54.

 A separate construct having IL-20RB fused to κ light was also constructed. The IL-20RB/human κ light chain construction was performed as above by PCRing from DR1/7N-4 with oligos SEQ ID NO: 50 and SEQ ID NO: 51, digesting
20 the resulting band with EcoRI and KpnI and then ligating this product into a previously EcoRI and KpnI digested and band-purified Vec#77 (above). The resulting vector was sequenced to confirm that the IL-20RB/ human κ light chain fusion (IL-20RB/ κ light) was correct. This IL-20RB// κ light construct is shown by SEQ ID NOs: 56 and 57. N-terminal sequencing of the resultant polypeptide indicated the presence of the predicted
25 mature amino acid sequence comprised of SEQ ID NO: 58. SEQ ID NO:59 is the mature portion of the extracellular domain of IL-20RB used.

Co-expression of the human IL-20RA and human IL-20RB receptors

 Approximately 16 μ g of each of vectors #194 and #195, above, were co-
30 transfected into BHK-570 cells (ATCC No. CRL-10314) using Lipofectamine™ reagent (Gibco/BRL), as per manufacturer's instructions. The transfected cells were selected

for 10 days in DMEM + 5%FBS (Gibco/BRL) containing 1 μ M of methotrexate (MTX) (Sigma, St. Louis, MO) and 0.5mg/ml G418 (Gibco/BRL) for 10 days. The resulting pool of transfectants was selected again in 10 μ M MTX and 0.5mg/ml G418 for 10 days.

5 The resulting pool of doubly selected cells was used to generate protein. Three factories (Nunc, Denmark) of this pool were used to generate 8 L of serum free conditioned medium. This conditioned media was passed over a 1 ml protein-A column and eluted in (10) 750 microliter fractions. 4 of these fractions found to have the highest concentration were pooled and dialyzed (10 kD MW cutoff) against PBS.

10 Finally, the dialyzed material was analyzed by BCA (Pierce) and found to have a concentration of 317 μ g/ml. A total of 951 μ g was obtained from this 8 L purification.

Example 13

IL-20 Binding Activates STAT3 in the HaCaT Keratinocyte Cell Line

15 IL-20 binds cell lines transfected with both subunits of its receptor. However, these cell lines overexpress the IL-20 receptor relative to its normal level and their relevance to the physiological role of IL-20 is unclear. The human HaCaT keratinocyte cell line, which expresses endogenous IL-20RA and IL-20RB was used to examine IL-20 signal transduction in a biologically relevant cell type. HaCaT cells

20 were infected with recombinant adenovirus containing a reporter construct to allow detection of intracellular signaling. The construct consists of the firefly luciferase gene driven by promoter/enhancer sequences comprised of the serum response element (SRE) and signal transducers and activators of transduction elements (STATs). This assay system detects productive ligand-receptor interactions and indicates possible

25 downstream signal transduction components involved in receptor activation. Treatment with IL-20 alone resulted in a dose-dependent increase in luciferase activity with a half maximal response occurring at approximately 2.3 nM. Subsequent luciferase reporter assays using adenovirus vectors containing only the SRE element or only the STAT elements produced detectable reporter activation only through STATs .

30 To determine if other cytokines act in concert with IL-20, HaCaT cells were treated with IL-20 alone or in combination with a single submaximal dose of EGF,

IL-1 β , or TNF α . In the presence of each of these three proteins, IL-20 treatment resulted in a dose-dependent increase in luciferase activity. IL-20 in combination with IL-1 β results in a half-maximal response at approximately 0.5 nM, about five-fold lower than with IL-20 alone. In addition, activation of the reporter gene is detectable at
5 0.1 nM IL-20, a dose that is at least tenfold lower than the IL-20 dose required alone.

BHK cells transfected with IL-20RA, IL-20RB or both receptor subunits were used to determine whether receptor pairing was required for IL-20 stimulation of STAT-luciferase. As was the case with binding assays, only cells transfected with both receptor subunits responded to IL-20 and did so with a half-maximal response of 5.7
10 pM. We note that the IL-20 concentration for the half-maximal response in BHK cells is 400-fold lower than that for half-maximal response in HaCaT cells. It is likely that a lower concentration of IL-20 is needed for half-maximal response in BHK cells, as compared to HaCaT cells, due to higher receptor levels in the BHK IL-20 receptor transfectants.

15 A nuclear translocation assay was used to identify STAT proteins involved in IL-20 action. Both HaCaT cells, with endogenous IL-20 receptors, and BHK cells transfected with IL-20RA and IL-20RB, were treated with IL-20 protein and translocation of STAT3 and STAT1 transcription factors from the cytoplasm to the nucleus was assayed by immunofluorescence.

20 In unstimulated HaCaT cells, STAT3 staining was predominantly in the cytosol. Treatment of HaCaT cells with IL-20 resulted in a distinct accumulation of STAT3 in the nucleus. Nuclear translocation of STAT3 in response to increasing concentrations of IL-20 occurred with a half-maximal IL-20 concentration of 7 nM. In contrast to STAT3 translocation, HaCaT cells treated with IL-20 did not show any
25 detectable nuclear accumulation of STAT1.

BHK cells transfected with IL-20RA and IL-20RB were used to confirm that the IL-20 receptor was required for IL-20 stimulation of STAT3 nuclear translocation. In BHK cells lacking the IL-20 receptor, STAT3 remained cytosolic following treatment with IL-20. In contrast, in BHK cells transfected with the IL-20
30 receptor, STAT3 translocated to the nucleus in response to IL-20. Again, STAT1

remained cytosolic regardless of IL-20 treatment or IL-20 receptor expression. We conclude that the IL-20 receptor is required for IL-20-mediated STAT3 activation.

WHAT IS CLAIMED IS:

- 1 . A method for treating a mammal afflicted with a disease in which
an IL-20 polypeptide plays a role, wherein the IL-20 polypeptide is comprised of an
5 amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6,
7, 8 and 9, comprising:
administering antagonist of said IL-20 polypeptide to said individual.
- 2 . The method of claim 1 wherein the antagonist is selected from the
10 group consisting of an antibody, antibody fragment or single chain antibody that binds
to said IL-20 polypeptide, a soluble receptor that binds to said IL-20 polypeptide and an
antibody, antibody fragment or single chain antibody which binds to the soluble
receptor of IL-20 wherein said soluble receptor is comprised of an IL-20RA subunit and
an IL-20RB subunit.
15
- 3 . The method of claim 2 wherein the soluble receptor is a comprised
of the extracellular domain of IL-20RA and the extracellular domain of IL-20RB.
- 4 . The method of claim 3 wherein the extracellular domain of IL-
20 20RA is fused to a constant region heavy chain of an immunoglobulin (Ig) molecule,
and the extracellular domain of IL-20RB is fused to a constant region of a light chain of
an Ig molecule.
- 5 . The method of claim 2 wherein the antibody, antibody fragment or
25 single chain antibody, which binds to the IL-20 receptor, binds to the IL-20RA subunit.
- 6 . The method of claim 2 wherein the antibody, antibody fragment or
single chain antibody, which binds to the IL-20 receptor, binds to the IL-20RB subunit.

7. The method of claim 1 wherein the disease that the IL-20 polypeptide plays a role is a skin disease selected from the group consisting of psoriasis, eczema, atopic dermatitis and contact dermatitis.

5 8. The method of claim 1 wherein the disease that the IL-20 polypeptide plays a role is an inflammatory lung selected from the group consisting of adult respiratory disease, asthma, bronchitis and pneumonia.

 9. A method for promoting the expression of IL-8 in a cell comprising
10 bringing the cell into contact with IL-20.

 10. A method for increasing the expression of IL-8 in an individual comprising administering IL-20 to said individual.

15

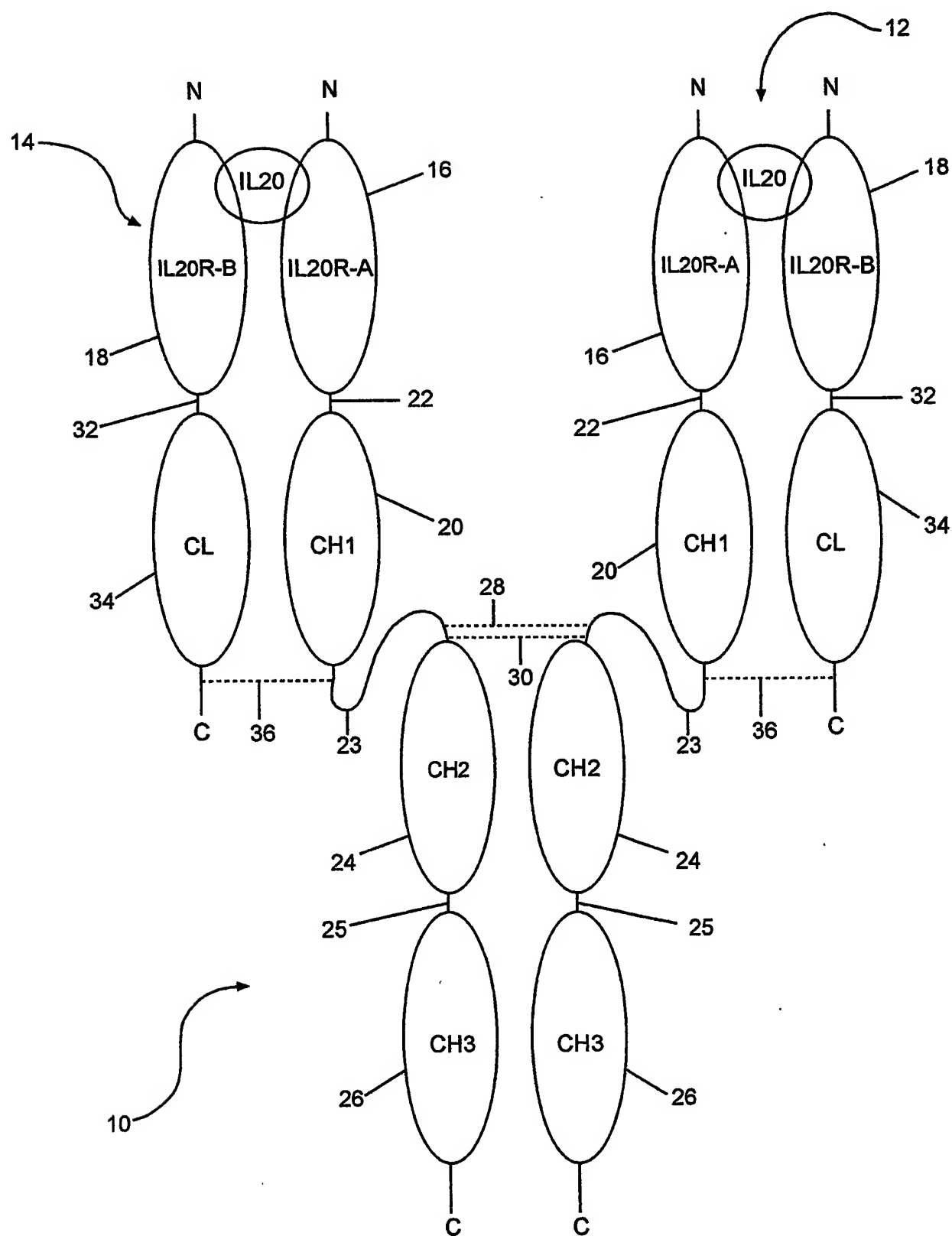


FIG.1

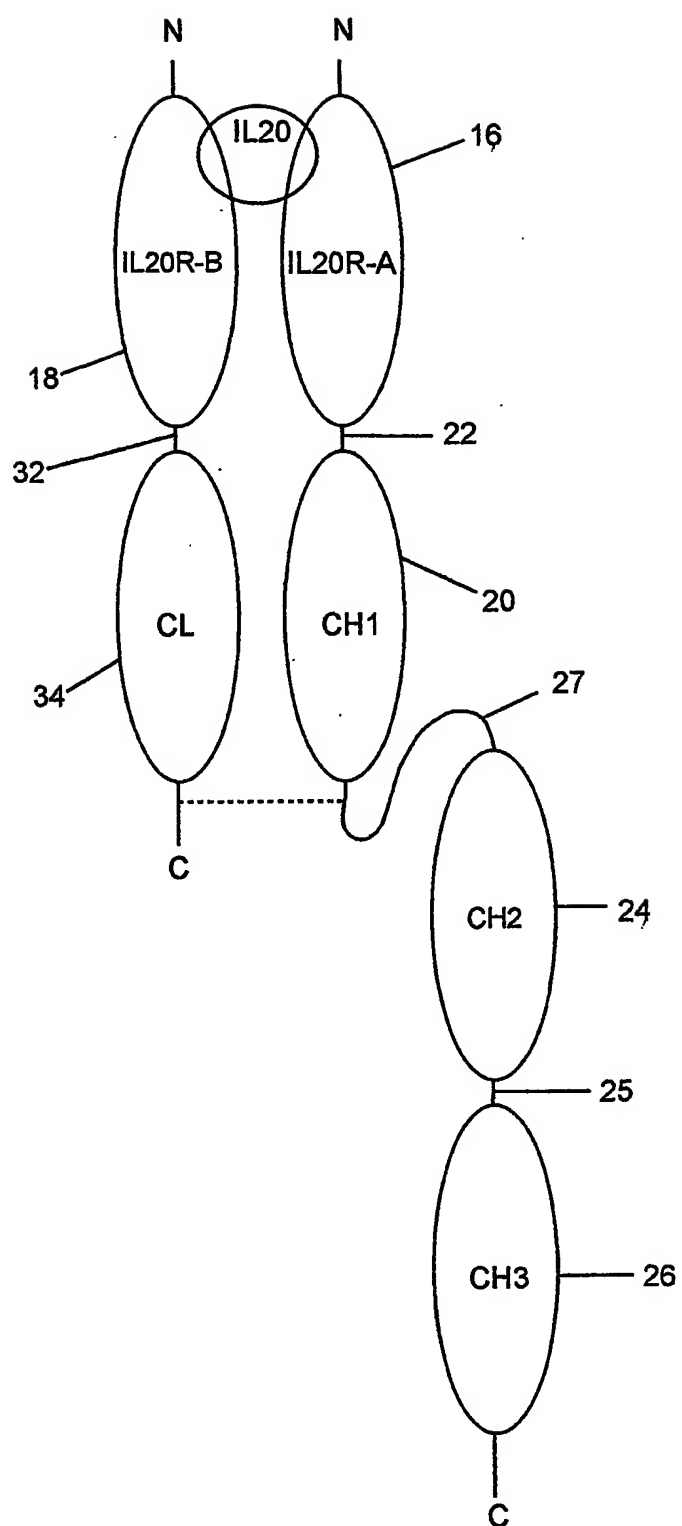


FIG.2

SUBSTITUTE SHEET (RULE 26)

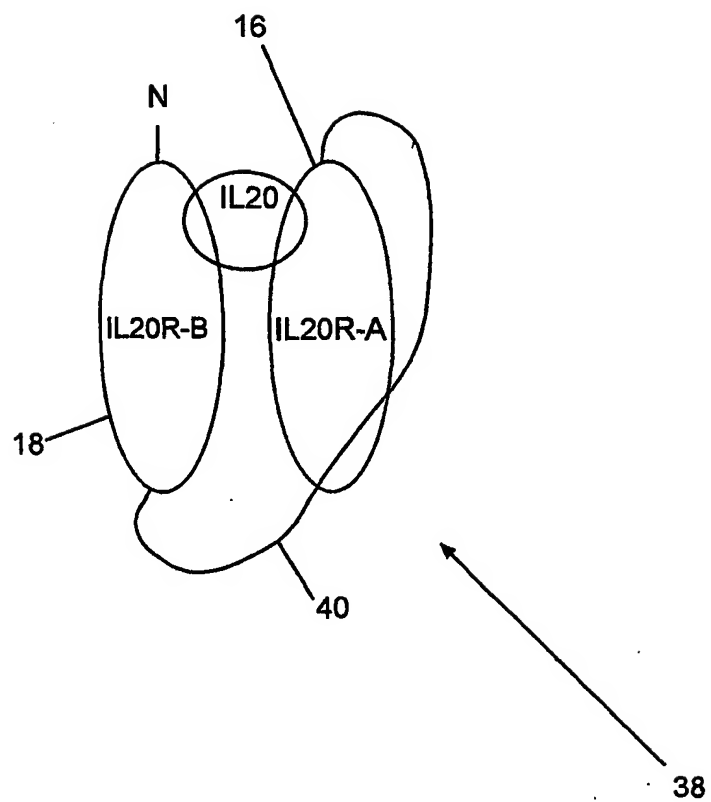


FIG.3

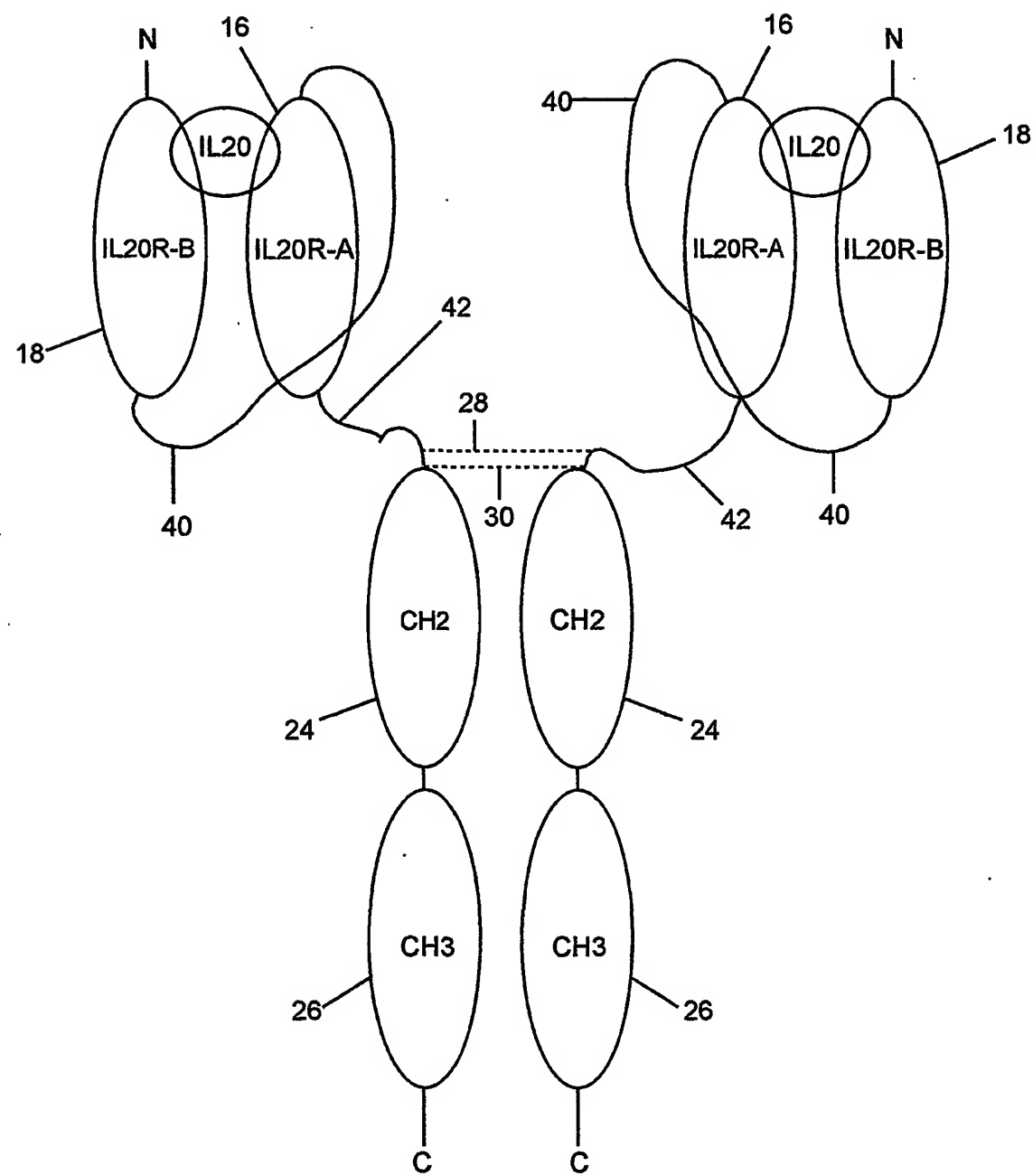


FIG.4

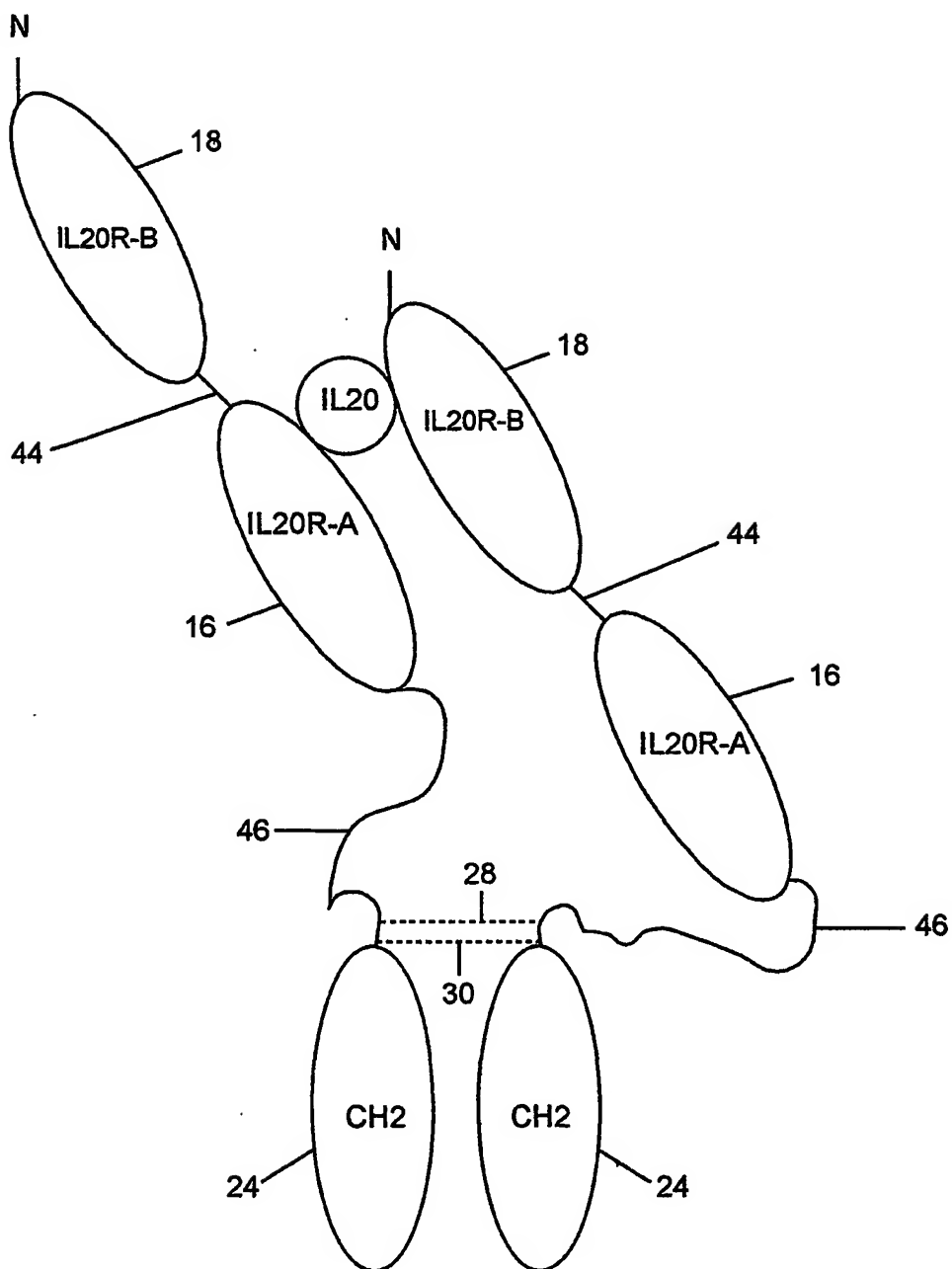


FIG.5

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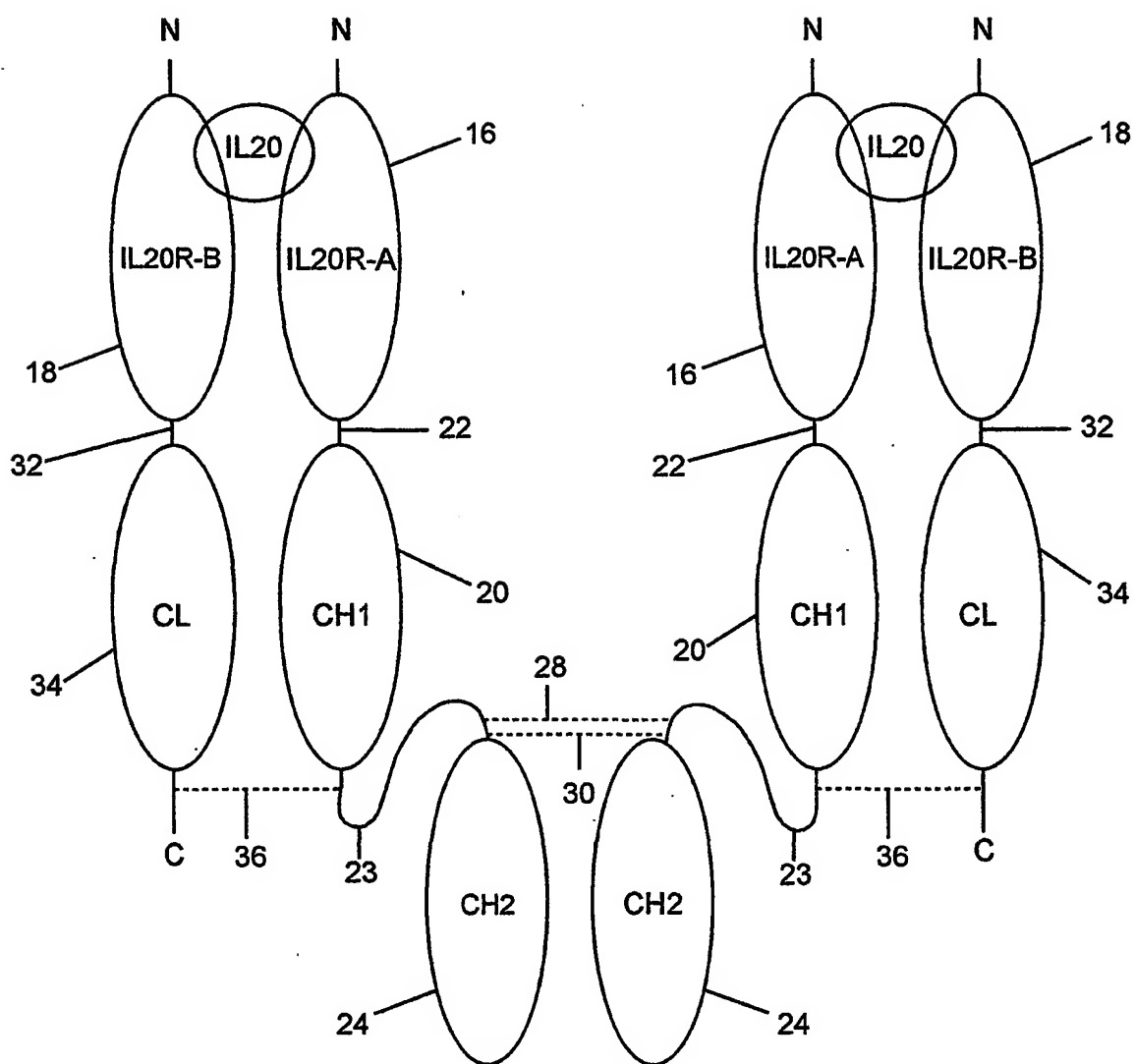


FIG.6

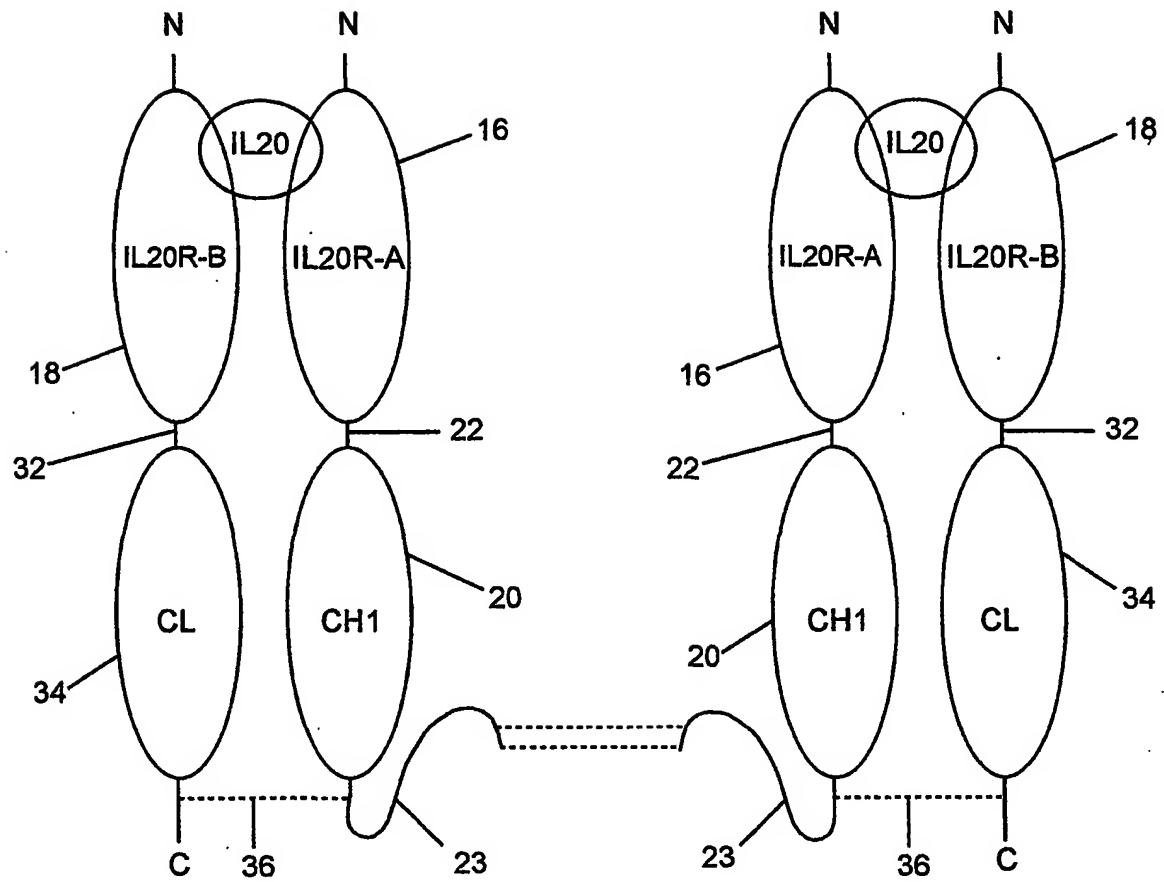


FIG.7

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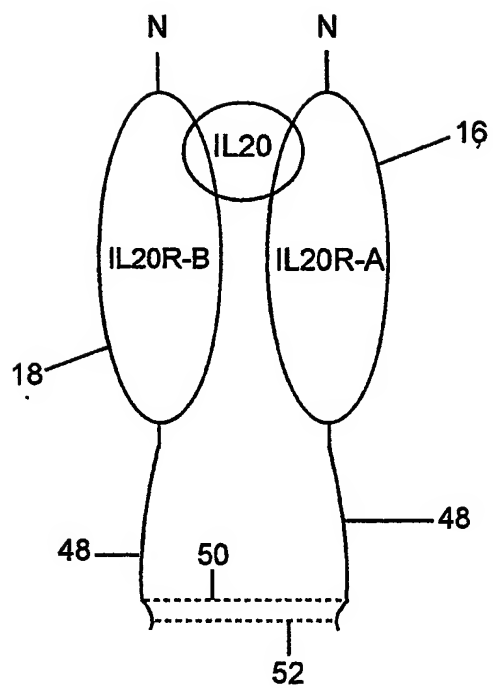


FIG.8

SEQUENCE LISTING

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agc ctt aat gat cct cag ccc agc ggg aac ctg agg ccc cct cag gag	1295
Ser Leu Asn Asp Pro Gln Pro Ser Gly Asn Leu Arg Pro Pro Gln Glu	
340 345 350	
gaa gag gag gtg aaa cat tta ggg tat gct tcg cat ttg atg gaa att	1343
Glu Glu Glu Val Lys His Leu Gly Tyr Ala Ser His Leu Met Glu Ile	
355 360 365	
ttt tgt gac tct gaa gaa aac acg gaa ggt act tct ttc acc cag caa	1391
Phe Cys Asp Ser Glu Glu Asn Thr Glu Gly Thr Ser Phe Thr Gln Gln	
370 375 380 385	
gag tcc ctc agc aga aca ata ccc ccg gat aaa aca gtc att gaa tat	1439
Glu Ser Leu Ser Arg Thr Ile Pro Pro Asp Lys Thr Val Ile Glu Tyr	
390 395 400	
gaa tat gat gtc aga acc act gac att tgt gcg ggg cct gaa gag cag	1487
Glu Tyr Asp Val Arg Thr Thr Asp Ile Cys Ala Gly Pro Glu Glu Gln	
405 410 415	
gag ctc agt ttg cag gag gag gtg tcc aca caa gga aca tta ttg gag	1535
Glu Leu Ser Leu Gln Glu Glu Val Ser Thr Gln Gly Thr Leu Leu Glu	
420 425 430	

tcg cag gca gcg ttg gca gtc ttg ggc ccg caa acg tta cag tac tca	1583
Ser Gln Ala Ala Leu Ala Val Leu Gly Pro Gln Thr Leu Gln Tyr Ser	
435 440 445	
tac acc cct cag ctc caa gac tta gac ccc ctg gcg cag gag cac aca	1631
Tyr Thr Pro Gln Leu Gln Asp Leu Asp Pro Leu Ala Gln Glu His Thr	
450 455 460 465	
gac tcg gag gag ggg ccg gag gaa gag cca tcg acg acc ctg gtc gac	1679
Asp Ser Glu Glu Gly Pro Glu Glu Glu Pro Ser Thr Thr Leu Val Asp	
470 475 480	
tgg gat ccc caa act ggc agg ctg tgt att cct tcg ctg tcc agc ttc	1727
Trp Asp Pro Gln Thr Gly Arg Leu Cys Ile Pro Ser Leu Ser Ser Phe	
485 490 495	
gac cag gat tca gag ggc tgc gag cct tct gag ggg gat ggg ctc gga	1775
Asp Gln Asp Ser Glu Gly Cys Glu Pro Ser Glu Gly Asp Gly Leu Gly	
500 505 510	
gag gag ggt ctt cta tct aga ctc tat gag gag ccg gct cca gac agg	1823
Glu Glu Gly Leu Leu Ser Arg Leu Tyr Glu Glu Pro Ala Pro Asp Arg	
515 520 525	
cca cca gga gaa aat gaa acc tat ctc atg caa ttc atg gag gaa tgg	1871
Pro Pro Gly Glu Asn Glu Thr Tyr Leu Met Gln Phe Met Glu Glu Trp	
530 535 540 545	
ggg tta tat gtg cag atg gaa aac tgatgccaac acttcctttt gccttttgtt	1925
Gly Leu Tyr Val Gln Met Glu Asn	
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tcctgtgcaa acaagtgagt cacccttttg atcccagcca taaagtacct gggatgaaag	1985
aagttttttc cagtttgtca gtgtctgtga gaattactta tttcttttct ctattctcat	2045
agcacgtgtg tgattggttc atgcatgtag gtctcttaac aatgatggtg ggcctctgga	2105
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gatggattct ggggtcatga cctttcgtga ttatccgcaa atgcaaacag tttcagatct 3305
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tagaaacgat tctgctggtt ttgaagaaca gatgtattac actaactgta aaagtagttc 3425
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<210> 11

<211> 553

<212> PRT

<213> Homo sapiens

<400> 11

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Leu Leu Leu Leu Leu Leu Ala Ala Pro Trp Gly Arg Ala Val Pro Cys
          20          25          30
Val Ser Gly Gly Leu Pro Lys Pro Ala Asn Ile Thr Phe Leu Ser Ile
          35          40          45
Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu Gly Leu Gln Gly
          50          55          60
Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys
65          70          75          80
Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr Tyr Cys Asp
          85          90          95
Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr Ala Lys Val
          100         105         110
Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg
          115         120         125
Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu Val Ala Leu
          130         135         140
Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys
          145         150         155         160

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Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr
 165 170 175
 Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg
 180 185 190
 Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu Thr Trp Leu
 195 200 205
 Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe Val Pro Gly
 210 215 220
 Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu
 225 230 235 240
 Lys Asp Gln Ser Ser Glu Phe Lys Ala Lys Ile Ile Phe Trp Tyr Val
 245 250 255
 Leu Pro Ile Ser Ile Thr Val Phe Leu Phe Ser Val Met Gly Tyr Ser
 260 265 270
 Ile Tyr Arg Tyr Ile His Val Gly Lys Glu Lys His Pro Ala Asn Leu
 275 280 285
 Ile Leu Ile Tyr Gly Asn Glu Phe Asp Lys Arg Phe Phe Val Pro Ala
 290 295 300
 Glu Lys Ile Val Ile Asn Phe Ile Thr Leu Asn Ile Ser Asp Asp Ser
 305 310 315 320
 Lys Ile Ser His Gln Asp Met Ser Leu Leu Gly Lys Ser Ser Asp Val
 325 330 335
 Ser Ser Leu Asn Asp Pro Gln Pro Ser Gly Asn Leu Arg Pro Pro Gln
 340 345 350
 Glu Glu Glu Glu Val Lys His Leu Gly Tyr Ala Ser His Leu Met Glu
 355 360 365
 Ile Phe Cys Asp Ser Glu Glu Asn Thr Glu Gly Thr Ser Phe Thr Gln
 370 375 380
 Gln Glu Ser Leu Ser Arg Thr Ile Pro Pro Asp Lys Thr Val Ile Glu
 385 390 395 400
 Tyr Glu Tyr Asp Val Arg Thr Thr Asp Ile Cys Ala Gly Pro Glu Glu
 405 410 415
 Gln Glu Leu Ser Leu Gln Glu Glu Val Ser Thr Gln Gly Thr Leu Leu
 420 425 430
 Glu Ser Gln Ala Ala Leu Ala Val Leu Gly Pro Gln Thr Leu Gln Tyr
 435 440 445
 Ser Tyr Thr Pro Gln Leu Gln Asp Leu Asp Pro Leu Ala Gln Glu His
 450 455 460
 Thr Asp Ser Glu Glu Gly Pro Glu Glu Glu Pro Ser Thr Thr Leu Val
 465 470 475 480
 Asp Trp Asp Pro Gln Thr Gly Arg Leu Cys Ile Pro Ser Leu Ser Ser
 485 490 495

Phe Asp Gln Asp Ser Glu Gly Cys Glu Pro Ser Glu Gly Asp Gly Leu
 500 505 510
 Gly Glu Glu Gly Leu Leu Ser Arg Leu Tyr Glu Glu Pro Ala Pro Asp
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 Trp Gly Leu Tyr Val Gln Met Glu Asn
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<211> 221

<212> PRT

<213> Homo sapiens

<400> 12

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 Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
 35 40 45
 Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr
 50 55 60
 Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr
 65 70 75 80
 Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu
 85 90 95
 Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu
 100 105 110
 Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala
 115 120 125
 Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln
 130 135 140
 Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
 145 150 155 160
 Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
 165 170 175
 Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
 180 185 190
 Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala
 195 200 205
 Arg Thr Leu Lys Asp Gln Ser Ser Glu Phe Lys Ala Lys
 210 215 220

<210> 13
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 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (18)...(950)

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Trp Thr Ser Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu	
15 20 25	
ctc aca gat gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta	146
Leu Thr Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val	
30 35 40	
ctc tca acc aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg	194
Leu Ser Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala	
45 50 55	
cct gga gaa aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag	242
Pro Gly Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu	
60 65 70 75	
agc ctg tac acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc	290
Ser Leu Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu	
80 85 90	
act gaa ggt cct gag tgt gat gtc act gat gac atc acg gcc act gtg	338
Thr Glu Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val	
95 100 105	
cca tac aac ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc	386
Pro Tyr Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala	
110 115 120	

tgg agc atc ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc	434
Trp Ser Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr	
125 130 135	
cga cct ggg atg gag atc acc aaa gat ggc ttc cac ctg gtt att gag	482
Arg Pro Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu	
140 145 150 155	
ctg gag gac ctg ggg ccc cag ttt gag ttc ctt gtg gcc tac tgg agg	530
Leu Glu Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg	
160 165 170	
agg gag cct ggt gcc gag gaa cat gtc aaa atg gtg agg agt ggg ggt	578
Arg Glu Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly	
175 180 185	
att cca gtg cac cta gaa acc atg gag cca ggg gct gca tac tgt gtg	626
Ile Pro Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val	
190 195 200	
aag gcc cag aca ttc gtg aag gcc att ggg agg tac agc gcc ttc agc	674
Lys Ala Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser	
205 210 215	
cag aca gaa tgt gtg gag gtg caa gga gag gcc att ccc ctg gta ctg	722
Gln Thr Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu	
220 225 230 235	
gcc ctg ttt gcc ttt gtt ggc ttc atg ctg atc ctt gtg gtc gtg cca	770
Ala Leu Phe Ala Phe Val Gly Phe Met Leu Ile Leu Val Val Val Pro	
240 245 250	
ctg ttc gtc tgg aaa atg ggc cgg ctg ctc cag tac tcc tgt tgc ccc	818
Leu Phe Val Trp Lys Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro	
255 260 265	
gtg gtg gtc ctc cca gac acc ttg aaa ata acc aat tca ccc cag aag	866
Val Val Val Leu Pro Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Lys	
270 275 280	
tta atc agc tgc aga agg gag gag gtg gat gcc tgt gcc acg gct gtg	914
Leu Ile Ser Cys Arg Arg Glu Glu Val Asp Ala Cys Ala Thr Ala Val	
285 290 295	

atg tct cct gag gaa ctc ctc agg gcc tgg atc tca taggtttgcg 960
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<210> 14

<211> 311

<212> PRT

<213> Homo sapiens

<400> 14

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 Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45
 Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60
 Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
 65 70 75 80
 His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
 85 90 95
 Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
 100 105 110
 Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
 115 120 125
 His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
 130 135 140
 Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
 145 150 155 160
 Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala
 165 170 175
 Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
 180 185 190
 Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
 195 200 205
 Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
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 Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu Ala Leu Phe Ala Phe
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<210> 15
<211> 203
<212> PRT
<213> Homo sapiens
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Glu	Thr	Val	Tyr 35	Tyr	Ser	Val	Glu 40	Tyr	Gln	Gly	Glu	Tyr 45	Glu	Ser	Leu
Tyr	Thr 50	Ser	His	Ile	Trp	Ile 55	Pro	Ser	Ser	Trp	Cys 60	Ser	Leu	Thr	Glu
Gly 65	Pro	Glu	Cys	Asp	Val 70	Thr	Asp	Asp	Ile	Thr 75	Ala	Thr	Val	Pro	Tyr 80
Asn	Leu	Arg	Val 85	Arg	Ala	Thr	Leu	Gly 90	Ser	Gln	Thr	Ser	Ala 95	Trp	Ser
Ile	Leu	Lys	His 100	Pro	Phe	Asn	Arg	Asn 105	Ser	Thr	Ile	Leu	Thr 110	Arg	Pro
Gly	Met	Glu	Ile 115	Thr	Lys	Asp	Gly 120	Phe	His	Leu	Val	Ile 125	Glu	Leu	Glu
Asp	Leu 130	Gly	Pro	Gln	Phe	Glu 135	Phe	Leu	Val	Ala 140	Tyr	Trp	Arg	Arg	Glu
Pro 145	Gly	Ala	Glu	Glu	His	Val 150	Lys	Met	Val	Arg 155	Ser	Gly	Gly	Ile	Pro 160
Val	His	Leu	Glu 165	Thr	Met	Glu	Pro	Gly 170	Ala	Ala	Tyr	Cys	Val 175	Lys	Ala
Gln	Thr	Phe	Val 180	Lys	Ala	Ile	Gly 185	Arg	Tyr	Ser	Ala	Phe	Ser 190	Gln	Thr
Glu	Cys	Val 195	Glu	Val	Gln	Gly 200	Glu	Ala	Ile	Pro					

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 <213> Homo sapiens

<400> 16
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<210> 17
 <211> 32
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<400> 17
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<210> 18
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<220>
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 gagtctacca a atg cag act ttc aca atg gtt cta gaa gaa atc tgg aca 170

Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr
 1 5 10

agt ctt ttc atg tgg ttt ttc tac gca ttg att cca tgt ttg ctc aca 218
 Ser Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr
 15 20 25

gat gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca 266
 Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 30 35 40 45

acc aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga 314

Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly	
50 55 60	
gaa aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg	362
Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu	
65 70 75	
tac acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc act gaa	410
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu	
80 85 90	
ggt cct gag tgt gat gtc act gat gac atc acg gcc act gtg cca tac	458
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr	
95 100 105	
aac ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc tgg agc	506
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser	
110 115 120 125	
atc ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc cga cct	554
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro	
130 135 140	
ggg atg gag atc ccc aaa cat ggc ttc cac ctg gtt att gag ctg gag	602
Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu	
145 150 155	
gac ctg ggg ccc cag ttt gag ttc ctt gtg gcc tac tgg acg agg gag	650
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu	
160 165 170	
cct ggt gcc gag gaa cat gtc aaa atg gtg agg agt ggg ggt att cca	698
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro	
175 180 185	
gtg cac cta gaa acc atg gag cca ggg gct gca tac tgt gtg aag gcc	746
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala	
190 195 200 205	
cag aca ttc gtg aag gcc att ggg agg tac agc gcc ttc agc cag aca	794
Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr	
210 215 220	

gaa tgt gtg gag gtg caa gga gag gcc att ccc ctg gta ctg gcc ctg 842
 Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu Ala Leu
 225 230 235

ttt gcc ttt gtt ggc ttc atg ctg atc ctt gtg gtc gtg cca ctg ttc 890
 Phe Ala Phe Val Gly Phe Met Leu Ile Leu Val Val Val Pro Leu Phe
 240 245 250

gtc tgg aaa atg ggc cgg ctg ctc cag tac tcc tgt tgc ccc gtg gtg 938
 Val Trp Lys Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro Val Val
 255 260 265

gtc ctc cca gac acc ttg aaa ata acc aat tca ccc cag gtt aat cag 986
 Val Leu Pro Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Val Asn Gln
 270 275 280 285

ctg cag aag gga gga ggt gga tgc ctg tgc cac ggc tgt gat gtc tcc 1034
 Leu Gln Lys Gly Gly Gly Gly Cys Leu Cys His Gly Cys Asp Val Ser
 290 295 300

tgaggaactc ctcagggcct ggatctcata tcaggtttgc ggaagggccc aggtgaagcc 1094
 gagaacctgg tctgcatgac atggaaacca tgaggggaca agttgtgttt ctgttttccg 1154
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 tctagacttt gggcttccac ttgcttggt gagcaaccct gggaaaagtg acttcatccc 1334
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<211> 301

<212> PRT

<213> Homo sapiens

<400> 19

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Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45

Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60

Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
 65 70 75 80

His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
 85 90 95
 Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
 100 105 110
 Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
 115 120 125
 His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
 130 135 140
 Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
 145 150 155 160
 Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro Gly Ala
 165 170 175
 Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
 180 185 190
 Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
 195 200 205
 Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
 210 215 220
 Glu Val Gln Gly Glu Ala Ile Pro Leu Val Leu Ala Leu Phe Ala Phe
 225 230 235 240
 Val Gly Phe Met Leu Ile Leu Val Val Val Pro Leu Phe Val Trp Lys
 245 250 255
 Met Gly Arg Leu Leu Gln Tyr Ser Cys Cys Pro Val Val Val Leu Pro
 260 265 270
 Asp Thr Leu Lys Ile Thr Asn Ser Pro Gln Val Asn Gln Leu Gln Lys
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<211> 1081

<212> DNA

<213> Homo sapiens

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Leu Phe Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp	
15 20 25 30	
gaa gtg gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca acc	146
Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr	
35 40 45	
aac atg aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga gaa	194
Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu	
50 55 60	
aca gtg tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg tac	242
Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr	
65 70 75	
acg agc cac atc tgg atc ccc agc agc tgg tgc tca ctc act gaa ggt	290
Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly	
80 85 90	
cct gag tgt gat gtc act gat gac atc acg gcc act gtg cca tac aac	338
Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn	
95 100 105 110	
ctt cgt gtc agg gcc aca ttg ggc tca cag acc tca gcc tgg agc atc	386
Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile	
115 120 125	
ctg aag cat ccc ttt aat aga aac tca acc atc ctt acc cga cct ggg	434
Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly	
130 135 140	
atg gag atc ccc aaa cat ggc ttc cac ctg gtt att gag ctg gag gac	482
Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp	
145 150 155	
ctg ggg ccc cag ttt gag ttc ctt gtg gcc tac tgg acg agg gag cct	530
Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro	
160 165 170	
ggc gcc gag gaa cat gtc aaa atg gtg agg agt ggg ggt att cca gtg	578
Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val	
175 180 185 190	

cac cta gaa acc atg gag cca ggg gct gca tac tgt gtg aag gcc cag His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln 195 200 205	626
aca ttc gtg aag gcc att ggg agg tac agc gcc ttc agc cag aca gaa Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu 210 215 220	674
tgt gtg gag gtg caa gga gag gcc gga ggt ggt ggc agt gga ggc ggc Cys Val Glu Val Gln Gly Glu Ala Gly Gly Gly Gly Ser Gly Gly Gly 225 230 235	722
ggc agc gga ggc ggt ggc agt cga act gtg gct gca cca tct gtc ttc Gly Ser Gly Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val Phe 240 245 250	770
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 <211> 352
 <212> PRT
 <213> Homo sapiens

<400> 21

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Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
             35             40             45
Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
             50             55             60
Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
65             70             75             80
His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
             85             90             95
Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
             100            105            110
Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
             115            120            125
His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
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Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
145            150            155            160
Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro Gly Ala
             165            170            175
Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
             180            185            190
Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
             195            200            205
Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
             210            215            220
Glu Val Gln Gly Glu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
225            230            235            240
Gly Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
             245            250            255
Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
             260            265            270
Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
             275            280            285

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Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
 290 295 300
 Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
 305 310 315 320
 Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
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 Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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<210> 22

<211> 1801

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (8)...(1789)

<400> 22

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 Cys Gly Ala Val Phe Val Ser Leu Ser Gln Glu Ile His Ala Glu Leu
 15 20 25 30

aga cgc ttc cgt aga gtt ccc tgt gtc tct ggt ggt ttg cct aaa cct 145
 Arg Arg Phe Arg Arg Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro
 35 40 45

gca aac atc acc ttc tta tcc atc aac atg aag aat gtc cta caa tgg 193
 Ala Asn Ile Thr Phe Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp
 50 55 60

act cca cca gag ggt ctt caa gga gtt aaa gtt act tac act gtg cag 241
 Thr Pro Pro Glu Gly Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln
 65 70 75

tat ttc ata tat ggg caa aag aaa tgg ctg aat aaa tca gaa tgc aga 289
 Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg
 80 85 90

aat atc aat aga acc tac tgt gat ctt tct gct gaa act tct gac tac	337
Asn Ile Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr	
95 100 105 110	
gaa cac cag tat tat gcc aaa gtt aag gcc att tgg gga aca aag tgt	385
Glu His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys	
115 120 125	
tcc aaa tgg gct gaa agt gga cgg ttc tat cct ttt tta gaa aca caa	433
Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln	
130 135 140	
att ggc cca cca gag gtg gca ctg act aca gat gag aag tcc att tct	481
Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser	
145 150 155	
gtt gtc ctg aca gct cca gag aag tgg aag aga aat cca gaa gac ctt	529
Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu	
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cct gtt tcc atg caa caa ata tac tcc aat ctg aag tat aac gtg tct	577
Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser	
175 180 185 190	
gtg ttg aat act aaa tca aac aga acg tgg tcc cag tgt gtg acc aac	625
Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn	
195 200 205	
cac acg ctg gtg ctc acc tgg ctg gag ccg aac act ctt tac tgc gta	673
His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val	
210 215 220	
cac gtg gag tcc ttc gtc cca ggg ccc cct cgc cgt gct cag cct tct	721
His Val Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser	
225 230 235	
gag aag cag tgt gcc agg act ttg aaa gat caa ggt gga ggc ggt tca	769
Glu Lys Gln Cys Ala Arg Thr Leu Lys Asp Gln Gly Gly Gly Gly Ser	
240 245 250	
ggc gga ggt ggc tct ggc ggt ggc gga tcg gcc tcc acc aag ggc cca	817
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Thr Lys Gly Pro	
255 260 265 270	

tcg gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggg ggc aca	865
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr	
275 280 285	
gcg gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg gtg acg	913
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr	
290 295 300	
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Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro	
305 310 315	
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Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr	
320 325 330	
gtg ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat	1057
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn	
335 340 345 350	
cac aag ccc agc aac acc aag gtg gac aag aaa gtt gag ccc aaa tct	1105
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser	
355 360 365	
tgt gac aaa act cac aca tgc cca ccg tgc cca gca cct gaa gcc gag	1153
Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu	
370 375 380	
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Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu	
385 390 395	
atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc	1249
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser	
400 405 410	
cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag	1297
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu	
415 420 425 430	
gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg	1345

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr	
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Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn	
450 455 460	
ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca tcc tcc	1441
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser	
465 470 475	
atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag	1489
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln	
480 485 490	
gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc	1537
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val	
495 500 505 510	
agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg	1585
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val	
515 520 525	
gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct	1633
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro	
530 535 540	
ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc	1681
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr	
545 550 555	
gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg	1729
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val	
560 565 570	
atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg	1777
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tct ccg ggt aaa taatctagat ct	1801
Ser Pro Gly Lys	

<211> 594

<212> PRT

<213> Homo sapiens

<400> 23

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Phe Arg Arg Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro Ala Asn
 35           40           45
Ile Thr Phe Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp Thr Pro
 50           55           60
Pro Glu Gly Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe
 65           70           75           80
Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile
 85           90           95
Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His
 100          105          110
Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys
 115          120          125
Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly
 130          135          140
Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val
 145          150          155          160
Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val
 165          170          175
Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu
 180          185          190
Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr
 195          200          205
Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val
 210          215          220
Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys
 225          230          235          240
Gln Cys Ala Arg Thr Leu Lys Asp Gln Gly Gly Gly Ser Gly Gly
 245          250          255
Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Thr Lys Gly Pro Ser Val
 260          265          270
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 275          280          285
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 290          295          300

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Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 305 310 315 320
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 325 330 335
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 340 345 350
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 355 360 365
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala
 370 375 380
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 385 390 395 400
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 405 410 415
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 420 425 430
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 435 440 445
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 450 455 460
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu
 465 470 475 480
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 485 490 495
 Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
 500 505 510
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 515 520 525
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 530 535 540
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 545 550 555 560
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 565 570 575
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 580 585 590
 Gly Lys

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<211> 29

<212> DNA

<213> Homo sapiens

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<210> 35
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<210> 36

<211> 1806

<212> DNA

<213> Mus musculus

<220>

<221> CDS

<222> (38)...(1675)

<400> 36

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Pro Ala Pro Gly His Pro Asp Pro Pro Pro Leu Leu Leu Leu Thr Leu
10 15 20

ctt ctg ctg ctg gcc gct tcg gga cgc gca gtt cct tgt gtc ttc tgt 151
Leu Leu Leu Leu Ala Ala Ser Gly Arg Ala Val Pro Cys Val Phe Cys
25 30 35

ggt ttg cct aaa cct aca aat atc acc ttc tta tcc atc aac atg aag 199
Gly Leu Pro Lys Pro Thr Asn Ile Thr Phe Leu Ser Ile Asn Met Lys
40 45 50

aat gtc ctg cat tgg aat cca cca gag agt cta cac gga gtt gaa gtc 247
Asn Val Leu His Trp Asn Pro Pro Glu Ser Leu His Gly Val Glu Val
55 60 65 70

aca tac act gtg caa tat ttc ata tat ggg cag aag aaa tgg ctg aat 295
Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn
75 80 85

gcc tct aaa tgc ggg agt atc aac agg acc tac tgt gac ctt tct gtt 343
Ala Ser Lys Cys Gly Ser Ile Asn Arg Thr Tyr Cys Asp Leu Ser Val
90 95 100

gag acc tca gac tat gaa cac cag ttc tat gcc aaa gtg aag gcc att Glu Thr Ser Asp Tyr Glu His Gln Phe Tyr Ala Lys Val Lys Ala Ile 105 110 115	391
tgg gaa gcc agg tgc tcc gaa tgg gcc gag acg gaa cgc ttc tat cct Trp Glu Ala Arg Cys Ser Glu Trp Ala Glu Thr Glu Arg Phe Tyr Pro 120 125 130	439
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aag tac aat gtg tct gtg tat aac act aag tcg aga aga acg tgg tcc Lys Tyr Asn Val Ser Val Tyr Asn Thr Lys Ser Arg Arg Thr Trp Ser 185 190 195	631
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cca aag gat atg aat tta ctg gac aaa agc agt gat gac atc agt gtt Pro Lys Asp Met Asn Leu Leu Asp Lys Ser Ser Asp Asp Ile Ser Val 330 335 340	1063
aat gac cct gag cac aat gag gcc tgg gag ccg cac tgg gag gag gtg Asn Asp Pro Glu His Asn Glu Ala Trp Glu Pro His Trp Glu Glu Val 345 350 355	1111
gag ggg caa cat tta gga tgc tct tcg cat ttg atg gac gct gtc tgt Glu Gly Gln His Leu Gly Cys Ser Ser His Leu Met Asp Ala Val Cys 360 365 370	1159
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Thr Ser Ala Asn Leu Asp Pro Gln Leu Glu Asp Leu His His Leu Gly
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 Gln Glu His Thr Val Ser Glu Asp Gly Pro Glu Glu Glu Thr Ser Ile
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 aca gta gtg gat tgg gac cct caa act ggc agg ctg tgt atc cct tcc 1495
 Thr Val Val Asp Trp Asp Pro Gln Thr Gly Arg Leu Cys Ile Pro Ser
 475 480 485
 tta cct atc ttt ggc cgt gat cct gag aac tat ggt cat tat gag aga 1543
 Leu Pro Ile Phe Gly Arg Asp Pro Glu Asn Tyr Gly His Tyr Glu Arg
 490 495 500
 gac cag ctc tta gag ggt ggc ctt ttg tct aga ctc tat gag aac cag 1591
 Asp Gln Leu Leu Glu Gly Gly Leu Leu Ser Arg Leu Tyr Glu Asn Gln
 505 510 515
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 Ala Pro Asp Lys Pro Glu Lys Glu Asn Glu Asn Cys Leu Thr Arg Phe
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 Met Glu Glu Trp Gly Leu His Val Gln Met Glu Ser
 535 540 545
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<210> 37

<211> 546

<212> PRT

<213> Mus musculus

<400> 37

Met His Thr Pro Gly Thr Pro Ala Pro Gly His Pro Asp Pro Pro Pro
 1 5 10 15
 Leu Leu Leu Leu Thr Leu Leu Leu Leu Ala Ala Ser Gly Arg Ala
 20 25 30
 Val Pro Cys Val Phe Cys Gly Leu Pro Lys Pro Thr Asn Ile Thr Phe
 35 40 45

Leu Ser Ile Asn Met Lys Asn Val Leu His Trp Asn Pro Pro Glu Ser
 50 55 60
 Leu His Gly Val Glu Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
 65 70 75 80
 Gln Lys Lys Trp Leu Asn Ala Ser Lys Cys Gly Ser Ile Asn Arg Thr
 85 90 95
 Tyr Cys Asp Leu Ser Val Glu Thr Ser Asp Tyr Glu His Gln Phe Tyr
 100 105 110
 Ala Lys Val Lys Ala Ile Trp Glu Ala Arg Cys Ser Glu Trp Ala Glu
 115 120 125
 Thr Glu Arg Phe Tyr Pro Phe Leu Glu Thr Gln Val Ser Pro Pro Glu
 130 135 140
 Ile Ala Leu Thr Thr Gly Glu Lys Ser Ile Ser Ile Ala Leu Thr Ala
 145 150 155 160
 Pro Glu Lys Trp Lys Arg Asn Pro Gln Asp His Thr Val Ser Met Gln
 165 170 175
 Gln Ile Tyr Pro Asn Leu Lys Tyr Asn Val Ser Val Tyr Asn Thr Lys
 180 185 190
 Ser Arg Arg Thr Trp Ser Gln Cys Val Thr Asn Ser Thr Leu Val Leu
 195 200 205
 Ser Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Leu
 210 215 220
 Val Pro Gly Pro Pro Arg Leu Pro Met Pro Ser Gln Lys Gln Cys Ile
 225 230 235 240
 Ser Thr Leu Glu Val Gln Thr Ser Ala Trp Lys Ala Lys Val Ile Phe
 245 250 255
 Trp Tyr Val Phe Leu Thr Ser Val Ile Val Phe Leu Phe Ser Ala Ile
 260 265 270
 Gly Tyr Leu Val Tyr Arg Tyr Ile His Val Gly Lys Glu Lys His Pro
 275 280 285
 Ala Asn Leu Val Leu Ile Tyr Arg Asn Glu Ile Gly Thr Arg Val Phe
 290 295 300
 Glu Pro Thr Glu Thr Ile Thr Leu Asn Phe Ile Thr Phe Ser Met Leu
 305 310 315 320
 Asp Asp Thr Lys Ile Ser Pro Lys Asp Met Asn Leu Leu Asp Lys Ser
 325 330 335
 Ser Asp Asp Ile Ser Val Asn Asp Pro Glu His Asn Glu Ala Trp Glu
 340 345 350
 Pro His Trp Glu Glu Val Glu Gly Gln His Leu Gly Cys Ser Ser His
 355 360 365
 Leu Met Asp Ala Val Cys Gly Ala Glu Gln Arg Asp Gly Asp Thr Ser
 370 375 380

Leu Thr Gln His Gly Trp Leu Asn Ser Thr Ile Pro Thr Gly Glu Thr
 385 390 395 400
 Asp Thr Glu Pro Gln Tyr Lys Val Leu Ser Asp Phe Tyr Gly Glu Gly
 405 410 415
 Glu Ile Gln Leu Ser Cys Glu Pro Glu Glu Ala Ala Arg Thr Glu Lys
 420 425 430
 Ile Ser Glu Pro Leu Val Thr Ser Ala Asn Leu Asp Pro Gln Leu Glu
 435 440 445
 Asp Leu His His Leu Gly Gln Glu His Thr Val Ser Glu Asp Gly Pro
 450 455 460
 Glu Glu Glu Thr Ser Ile Thr Val Val Asp Trp Asp Pro Gln Thr Gly
 465 470 475 480
 Arg Leu Cys Ile Pro Ser Leu Pro Ile Phe Gly Arg Asp Pro Glu Asn
 485 490 495
 Tyr Gly His Tyr Glu Arg Asp Gln Leu Leu Glu Gly Gly Leu Leu Ser
 500 505 510
 Arg Leu Tyr Glu Asn Gln Ala Pro Asp Lys Pro Glu Lys Glu Asn Glu
 515 520 525
 Asn Cys Leu Thr Arg Phe Met Glu Glu Trp Gly Leu His Val Gln Met
 530 535 540
 Glu Ser
 545

<210> 38

<211> 217

<212> PRT

<213> Mus musculus

<400> 38

Val Pro Cys Val Phe Cys Gly Leu Pro Lys Pro Thr Asn Ile Thr Phe
 1 5 10 15
 Leu Ser Ile Asn Met Lys Asn Val Leu His Trp Asn Pro Pro Glu Ser
 20 25 30
 Leu His Gly Val Glu Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
 35 40 45
 Gln Lys Lys Trp Leu Asn Ala Ser Lys Cys Gly Ser Ile Asn Arg Thr
 50 55 60
 Tyr Cys Asp Leu Ser Val Glu Thr Ser Asp Tyr Glu His Gln Phe Tyr
 65 70 75 80
 Ala Lys Val Lys Ala Ile Trp Glu Ala Arg Cys Ser Glu Trp Ala Glu
 85 90 95
 Thr Glu Arg Phe Tyr Pro Phe Leu Glu Thr Gln Val Ser Pro Pro Glu
 100 105 110

Ile	Ala	Leu	Thr	Thr	Gly	Glu	Lys	Ser	Ile	Ser	Ile	Ala	Leu	Thr	Ala
	115						120					125			
Pro	Glu	Lys	Trp	Lys	Arg	Asn	Pro	Gln	Asp	His	Thr	Val	Ser	Met	Gln
	130					135					140				
Gln	Ile	Tyr	Pro	Asn	Leu	Lys	Tyr	Asn	Val	Ser	Val	Tyr	Asn	Thr	Lys
145					150					155					160
Ser	Arg	Arg	Thr	Trp	Ser	Gln	Cys	Val	Thr	Asn	Ser	Thr	Leu	Val	Leu
				165					170					175	
Ser	Trp	Leu	Glu	Pro	Asn	Thr	Leu	Tyr	Cys	Val	His	Val	Glu	Ser	Leu
			180					185					190		
Val	Pro	Gly	Pro	Pro	Arg	Leu	Pro	Met	Pro	Ser	Gln	Lys	Gln	Cys	Ile
	195						200					205			
Ser	Thr	Leu	Glu	Val	Gln	Thr	Ser	Ala							
	210					215									

<210> 39
<211> 514
<212> PRT
<213> Mus musculus

<400> 39															
Val	Pro	Cys	Val	Phe	Cys	Gly	Leu	Pro	Lys	Pro	Thr	Asn	Ile	Thr	Phe
1			5					10					15		
Leu	Ser	Ile	Asn	Met	Lys	Asn	Val	Leu	His	Trp	Asn	Pro	Pro	Glu	Ser
			20					25					30		
Leu	His	Gly	Val	Glu	Val	Thr	Tyr	Thr	Val	Gln	Tyr	Phe	Ile	Tyr	Gly
		35					40					45			
Gln	Lys	Lys	Trp	Leu	Asn	Ala	Ser	Lys	Cys	Gly	Ser	Ile	Asn	Arg	Thr
	50					55					60				
Tyr	Cys	Asp	Leu	Ser	Val	Glu	Thr	Ser	Asp	Tyr	Glu	His	Gln	Phe	Tyr
65					70					75					80
Ala	Lys	Val	Lys	Ala	Ile	Trp	Glu	Ala	Arg	Cys	Ser	Glu	Trp	Ala	Glu
				85					90					95	
Thr	Glu	Arg	Phe	Tyr	Pro	Phe	Leu	Glu	Thr	Gln	Val	Ser	Pro	Pro	Glu
			100					105					110		
Ile	Ala	Leu	Thr	Thr	Gly	Glu	Lys	Ser	Ile	Ser	Ile	Ala	Leu	Thr	Ala
		115					120					125			
Pro	Glu	Lys	Trp	Lys	Arg	Asn	Pro	Gln	Asp	His	Thr	Val	Ser	Met	Gln
	130					135					140				
Gln	Ile	Tyr	Pro	Asn	Leu	Lys	Tyr	Asn	Val	Ser	Val	Tyr	Asn	Thr	Lys
145					150					155					160
Ser	Arg	Arg	Thr	Trp	Ser	Gln	Cys	Val	Thr	Asn	Ser	Thr	Leu	Val	Leu
				165					170					175	

Ser Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Leu
 180 185 190
 Val Pro Gly Pro Pro Arg Leu Pro Met Pro Ser Gln Lys Gln Cys Ile
 195 200 205
 Ser Thr Leu Glu Val Gln Thr Ser Ala Trp Lys Ala Lys Val Ile Phe
 210 215 220
 Trp Tyr Val Phe Leu Thr Ser Val Ile Val Phe Leu Phe Ser Ala Ile
 225 230 235 240
 Gly Tyr Leu Val Tyr Arg Tyr Ile His Val Gly Lys Glu Lys His Pro
 245 250 255
 Ala Asn Leu Val Leu Ile Tyr Arg Asn Glu Ile Gly Thr Arg Val Phe
 260 265 270
 Glu Pro Thr Glu Thr Ile Thr Leu Asn Phe Ile Thr Phe Ser Met Leu
 275 280 285
 Asp Asp Thr Lys Ile Ser Pro Lys Asp Met Asn Leu Leu Asp Lys Ser
 290 295 300
 Ser Asp Asp Ile Ser Val Asn Asp Pro Glu His Asn Glu Ala Trp Glu
 305 310 315 320
 Pro His Trp Glu Glu Val Glu Gly Gln His Leu Gly Cys Ser Ser His
 325 330 335
 Leu Met Asp Ala Val Cys Gly Ala Glu Gln Arg Asp Gly Asp Thr Ser
 340 345 350
 Leu Thr Gln His Gly Trp Leu Asn Ser Thr Ile Pro Thr Gly Glu Thr
 355 360 365
 Asp Thr Glu Pro Gln Tyr Lys Val Leu Ser Asp Phe Tyr Gly Glu Gly
 370 375 380
 Glu Ile Gln Leu Ser Cys Glu Pro Glu Glu Ala Ala Arg Thr Glu Lys
 385 390 395 400
 Ile Ser Glu Pro Leu Val Thr Ser Ala Asn Leu Asp Pro Gln Leu Glu
 405 410 415
 Asp Leu His His Leu Gly Gln Glu His Thr Val Ser Glu Asp Gly Pro
 420 425 430
 Glu Glu Glu Thr Ser Ile Thr Val Val Asp Trp Asp Pro Gln Thr Gly
 435 440 445
 Arg Leu Cys Ile Pro Ser Leu Pro Ile Phe Gly Arg Asp Pro Glu Asn
 450 455 460
 Tyr Gly His Tyr Glu Arg Asp Gln Leu Leu Glu Gly Gly Leu Leu Ser
 465 470 475 480
 Arg Leu Tyr Glu Asn Gln Ala Pro Asp Lys Pro Glu Lys Glu Asn Glu
 485 490 495
 Asn Cys Leu Thr Arg Phe Met Glu Glu Trp Gly Leu His Val Gln Met
 500 505 510
 Glu Ser

<210> 40
<211> 18
<212> DNA
<213> Mus musculus

<400> 40
cgccgcgttc ccgagatg 18

<210> 41
<211> 24
<212> DNA
<213> Mus musculus

<400> 41
ggatgaggca gggctgacaa agtt 24

<210> 42
<211> 36
<212> DNA
<213> Homo sapiens

<400> 42
acttgaggaa ttcgctagca ccaagggccc atcggg 36

<210> 43
<211> 32
<212> DNA
<213> Homo sapiens

<400> 43
gcctagaacg cgttcattta cccggagaca gg 32

<210> 44
<211> 8
<212> DNA
<213> Homo sapiens

<400> 44
aattgaga 8

<210> 45
<211> 8

<212> DNA

<213> Homo sapiens

<400> 45

cgcgctctc

8

<210> 46

<211> 37

<212> DNA

<213> Homo sapiens

<400> 46

gtcacttgaa ttcggtaccg cctctgttgt gtgcctg

37

<210> 47

<211> 32

<212> DNA

<213> Homo sapiens

<400> 47

gacctgaacg cgtctaacac tctcccctgt tg

32

<210> 48

<211> 38

<212> DNA

<213> Homo sapiens

<400> 48

tcagtcggaa ttcgcagaag ccatgcgggc tcccgcc

38

<210> 49

<211> 35

<212> DNA

<213> Homo sapiens

<400> 49

ctgtgacgct agcctctgat gattgatctt tcaaa

35

<210> 50

<211> 43

<212> DNA

<213> Homo sapiens

<400> 50
 gatgtctgaa ttgcgagaag ccatgcagac tttcacaatg gtt 43

<210> 51
 <211> 86
 <212> DNA
 <213> Homo sapiens

<400> 51
 aagacggtac cagatttcaa ctgctcatca gatggcggga agatgaagac agatggtgca 60
 gccacagtgg cctctccttg cacctc 86

<210> 52
 <211> 1720
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)...(1713)

<400> 52
 atg cgg gct ccc ggc cgc ccg gcc ctg cgg ccg ctg ctg ctg ttg ctc 48
 Met Arg Ala Pro Gly Arg Pro Ala Leu Arg Pro Leu Leu Leu Leu Leu
 1 5 10 15

ctg gcg gcg cct tgg gga cgg gca gtt ccc tgt gtc tct ggt ggt ttg 96
 Leu Ala Ala Pro Trp Gly Arg Ala Val Pro Cys Val Ser Gly Gly Leu
 20 25 30

cct aaa cct gca aac atc acc ttc tta tcc atc aac atg aag aat gtc 144
 Pro Lys Pro Ala Asn Ile Thr Phe Leu Ser Ile Asn Met Lys Asn Val
 35 40 45

cta caa tgg act cca cca gag ggt ctt caa gga gtt aaa gtt act tac 192
 Leu Gln Trp Thr Pro Pro Glu Gly Leu Gln Gly Val Lys Val Thr Tyr
 50 55 60

act gtg cag tat ttc ata tat ggg caa aag aaa tgg ctg aat aaa tca 240
 Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser
 65 70 75 80

gaa tgc aga aat atc aat aga acc tac tgt gat ctt tct gct gaa act 288

Glu Cys Arg Asn Ile Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr	
85 90 95	
tct gac tac gaa cac cag tat tat gcc aaa gtt aag gcc att tgg gga	336
Ser Asp Tyr Glu His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly	
100 105 110	
aca aag tgt tcc aaa tgg gct gaa agt gga cgg ttc tat cct ttt tta	384
Thr Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu	
115 120 125	
gaa aca caa att ggc cca cca gag gtg gca ctg act aca gat gag aag	432
Glu Thr Gln Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys	
130 135 140	
tcc att tct gtt gtc ctg aca gct cca gag aag tgg aag aga aat cca	480
Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro	
145 150 155 160	
gaa gac ctt cct gtt tcc atg caa caa ata tac tcc aat ctg aag tat	528
Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr	
165 170 175	
aac gtg tct gtg ttg aat act aaa tca aac aga acg tgg tcc cag tgt	576
Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys	
180 185 190	
gtg acc aac cac acg ctg gtg ctc acc tgg ctg gag ccg aac act ctt	624
Val Thr Asn His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu	
195 200 205	
tac tgc gta cac gtg gag tcc ttc gtc cca ggg ccc cct cgc cgt gct	672
Tyr Cys Val His Val Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala	
210 215 220	
cag cct tct gag aag cag tgt gcc agg act ttg aaa gat caa tca tca	720
Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu Lys Asp Gln Ser Ser	
225 230 235 240	
gag gct agc acc aag ggc cca tcg gtc ttc ccc ctg gca ccc tcc tcc	768
Glu Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser	
245 250 255	

aag agc acc tct ggg ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp 260 265 270	816
tac ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg acc Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr 275 280 285	864
agc ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr 290 295 300	912
tcc ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acc cag Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln 305 310 315 320	960
acc tac atc tgc aac gtg aat cac aag ccc agc aac acc aag gtg gac Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp 325 330 335	1008
aag aaa gtt gag ccc aaa tct tgt gac aaa act cac aca tgc cca ccg Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro 340 345 350	1056
tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro 355 360 365	1104
cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc aca Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr 370 375 380	1152
tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc aac Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn 385 390 395 400	1200
tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg 405 410 415	1248
gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val 420 425 430	1296

ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc tcc 1344
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 435 440 445

aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc aaa gcc aaa 1392
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 450 455 460

ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg gat 1440
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 465 470 475 480

gag ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc 1488
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 485 490 495

tat ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg gag 1536
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 500 505 510

aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc 1584
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 515 520 525

ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag ggg 1632
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 530 535 540

aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac tac 1680
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 545 550 555 560

acg cag aag agc ctc tcc ctg tct ccg ggt aaa tgacgcg 1720
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 565 570

<210> 53

<211> 571

<212> PRT

<213> Homo sapiens

<400> 53

Met Arg Ala Pro Gly Arg Pro Ala Leu Arg Pro Leu Leu Leu Leu Leu
 1 5 10 15
 Leu Ala Ala Pro Trp Gly Arg Ala Val Pro Cys Val Ser Gly Gly Leu
 20 25 30
 Pro Lys Pro Ala Asn Ile Thr Phe Leu Ser Ile Asn Met Lys Asn Val
 35 40 45
 Leu Gln Trp Thr Pro Pro Glu Gly Leu Gln Gly Val Lys Val Thr Tyr
 50 55 60
 Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser
 65 70 75 80
 Glu Cys Arg Asn Ile Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr
 85 90 95
 Ser Asp Tyr Glu His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly
 100 105 110
 Thr Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu
 115 120 125
 Glu Thr Gln Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys
 130 135 140
 Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro
 145 150 155 160
 Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr
 165 170 175
 Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys
 180 185 190
 Val Thr Asn His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu
 195 200 205
 Tyr Cys Val His Val Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala
 210 215 220
 Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu Lys Asp Gln Ser Ser
 225 230 235 240
 Glu Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
 245 250 255
 Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
 260 265 270
 Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
 275 280 285
 Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
 290 295 300
 Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
 305 310 315 320
 Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
 325 330 335

340 345 350
 Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 355 360 365
 Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
 370 375 380
 Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
 385 390 395 400
 Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
 405 410 415
 Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 420 425 430
 Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
 435 440 445
 Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
 450 455 460
 Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 465 470 475 480
 Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 485 490 495
 Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 500 505 510
 Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 515 520 525
 Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 530 535 540
 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 545 550 555 560
 Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 565 570

<210> 54

<211> 547

<212> PRT

<213> Homo sapiens

<400> 54

Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro Ala Asn Ile Thr Phe
 1 5 10 15
 Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu Gly
 20 25 30
 Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
 35 40 45

Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr
 50 55 60
 Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr
 65 70 75 80
 Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu
 85 90 95
 Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu
 100 105 110
 Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala
 115 120 125
 Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln
 130 135 140
 Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
 145 150 155 160
 Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
 165 170 175
 Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
 180 185 190
 Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala
 195 200 205
 Arg Thr Leu Lys Asp Gln Ser Ser Glu Ala Ser Thr Lys Gly Pro Ser
 210 215 220
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 225 230 235 240
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 245 250 255
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 260 265 270
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 275 280 285
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 290 295 300
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
 305 310 315 320
 Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 325 330 335
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 340 345 350
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 355 360 365
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 370 375 380

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 385 390 395 400
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 405 410 415
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 420 425 430
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 435 440 445
 Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 450 455 460
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 465 470 475 480
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 485 490 495
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 500 505 510
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 515 520 525
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 530 535 540
 Pro Gly Lys
 545

<210> 55

<211> 217

<212> PRT

<213> Homo sapiens

<400> 55

Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro Ala Asn Ile Thr Phe
 1 5 10 15
 Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu Gly
 20 25 30
 Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
 35 40 45
 Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr
 50 55 60
 Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr
 65 70 75 80
 Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu
 85 90 95
 Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu
 100 105 110

Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala
 115 120 125
 Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln
 130 135 140
 Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
 145 150 155 160
 Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
 165 170 175
 Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
 180 185 190
 Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala
 195 200 205
 Arg Thr Leu Lys Asp Gln Ser Ser Glu
 210 215

<210> 56
 <211> 1011
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)...(1008)

<400> 56
 atg cag act ttc aca atg gtt cta gaa gaa atc tgg aca agt ctt ttc 48
 Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr Ser Leu Phe
 1 5 10 15

 atg tgg ttt ttc tac gca ttg att cca tgt ttg ctc aca gat gaa gtg 96
 Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
 20 25 30

 gcc att ctg cct gcc cct cag aac ctc tct gta ctc tca acc aac atg 144
 Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45

 aag cat ctc ttg atg tgg agc cca gtg atc gcg cct gga gaa aca gtg 192
 Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60

 tac tat tct gtc gaa tac cag ggg gag tac gag agc ctg tac acg agc 240

Tyr	Tyr	Ser	Val	Glu	Tyr	Gln	Gly	Glu	Tyr	Glu	Ser	Leu	Tyr	Thr	Ser		
65					70					75					80		
cac	atc	tgg	atc	ccc	agc	agc	tgg	tgc	tca	ctc	act	gaa	ggt	cct	gag	288	
His	Ile	Trp	Ile	Pro	Ser	Ser	Trp	Cys	Ser	Leu	Thr	Glu	Gly	Pro	Glu		
				85				90						95			
tgt	gat	gtc	act	gat	gac	atc	acg	gcc	act	gtg	cca	tac	aac	ctt	cgt	336	
Cys	Asp	Val	Thr	Asp	Asp	Ile	Thr	Ala	Thr	Val	Pro	Tyr	Asn	Leu	Arg		
			100					105					110				
gtc	agg	gcc	aca	ttg	ggc	tca	cag	acc	tca	gcc	tgg	agc	atc	ctg	aag	384	
Val	Arg	Ala	Thr	Leu	Gly	Ser	Gln	Thr	Ser	Ala	Trp	Ser	Ile	Leu	Lys		
		115					120					125					
cat	ccc	ttt	aat	aga	aac	tca	acc	atc	ctt	acc	cga	cct	ggg	atg	gag	432	
His	Pro	Phe	Asn	Arg	Asn	Ser	Thr	Ile	Leu	Thr	Arg	Pro	Gly	Met	Glu		
	130					135					140						
atc	acc	aaa	gat	ggc	ttc	cac	ctg	gtt	att	gag	ctg	gag	gac	ctg	ggg	480	
Ile	Thr	Lys	Asp	Gly	Phe	His	Leu	Val	Ile	Glu	Leu	Glu	Asp	Leu	Gly		
145					150					155				160			
ccc	cag	ttt	gag	ttc	ctt	gtg	gcc	tac	tgg	agg	agg	gag	cct	ggt	gcc	528	
Pro	Gln	Phe	Glu	Phe	Leu	Val	Ala	Tyr	Trp	Arg	Arg	Glu	Pro	Gly	Ala		
				165					170					175			
gag	gaa	cat	gtc	aaa	atg	gtg	agg	agt	ggg	ggt	att	cca	gtg	cac	cta	576	
Glu	Glu	His	Val	Lys	Met	Val	Arg	Ser	Gly	Gly	Ile	Pro	Val	His	Leu		
			180					185					190				
gaa	acc	atg	gag	cca	ggg	gct	gca	tac	tgt	gtg	aag	gcc	cag	aca	ttc	624	
Glu	Thr	Met	Glu	Pro	Gly	Ala	Ala	Tyr	Cys	Val	Lys	Ala	Gln	Thr	Phe		
		195					200					205					
gtg	aag	gcc	att	ggg	agg	tac	agc	gcc	ttc	agc	cag	aca	gaa	tgt	gtg	672	
Val	Lys	Ala	Ile	Gly	Arg	Tyr	Ser	Ala	Phe	Ser	Gln	Thr	Glu	Cys	Val		
	210					215					220						
gag	gtg	caa	gga	gag	gcc	act	gtg	gct	gca	cca	tct	gtc	ttc	atc	ttc	720	
Glu	Val	Gln	Gly	Glu	Ala	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe		
225					230					235					240		

ccg cca tct gat gag cag ttg aaa tct ggt acc gcc tct gtt gtg tgc 768
 Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
 245 250 255

ctg ctg aat aac ttc tat ccc aga gag gcc aaa gta cag tgg aag gtg 816
 Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
 260 265 270

gat aac gcc ctc caa tcg ggt aac tcc cag gag agt gtc aca gag cag 864
 Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
 275 280 285

gac agc aag gac agc acc tac agc ctc agc agc acc ctg acg ctg agc 912
 Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
 290 295 300

aaa gca gac tac gag aaa cac aaa gtc tac gcc tgc gaa gtc acc cat 960
 Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
 305 310 315 320

cag ggc ctg agc tcg ccc gtc aca aag agc ttc aac agg gga gag tgt 1008
 Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 325 330 335

tag 1011

<210> 57

<211> 336

<212> PRT

<213> Homo sapiens

<400> 57

Met Gln Thr Phe Thr Met Val Leu Glu Glu Ile Trp Thr Ser Leu Phe
 1 5 10 15
 Met Trp Phe Phe Tyr Ala Leu Ile Pro Cys Leu Leu Thr Asp Glu Val
 20 25 30
 Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met
 35 40 45
 Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val
 50 55 60
 Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser
 65 70 75 80

His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu
 85 90 95
 Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg
 100 105 110
 Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys
 115 120 125
 His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu
 130 135 140
 Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly
 145 150 155 160
 Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu Pro Gly Ala
 165 170 175
 Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu
 180 185 190
 Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe
 195 200 205
 Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val
 210 215 220
 Glu Val Gln Gly Glu Ala Thr Val Ala Ala Pro Ser Val Phe Ile Phe
 225 230 235 240
 Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
 245 250 255
 Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
 260 265 270
 Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
 275 280 285
 Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
 290 295 300
 Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
 305 310 315 320
 Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 325 330 335

<210> 58

<211> 307

<212> PRT

<213> Homo sapiens

<400> 58

Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 1 5 10 15
 Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
 20 25 30

Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
 35 40 45
 Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
 50 55 60
 Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
 65 70 75 80
 Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
 85 90 95
 Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
 100 105 110
 Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu
 115 120 125
 Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu
 130 135 140
 Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
 145 150 155 160
 Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
 165 170 175
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 180 185 190
 Glu Cys Val Glu Val Gln Gly Glu Ala Thr Val Ala Ala Pro Ser Val
 195 200 205
 Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
 210 215 220
 Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
 225 230 235 240
 Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
 245 250 255
 Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
 260 265 270
 Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
 275 280 285
 Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg
 290 295 300
 Gly Glu Cys
 305

<210> 59

<211> 201

<212> PRT

<213> Homo sapiens

<400> 59

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Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 1           5           10           15
Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
          20           25           30
Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
          35           40           45
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
          50           55           60
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
65           70           75           80
Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
          85           90           95
Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
          100          105          110
Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu Val Ile Glu Leu Glu
          115          120          125
Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Arg Arg Glu
          130          135          140
Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
145          150          155          160
Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
          165          170          175
Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
          180          185          190
Glu Cys Val Glu Val Gln Gly Glu Ala
          195          200

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<210> 60

<211> 323

<212> PRT

<213> Homo sapiens

<400> 60

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Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 1           5           10           15
Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
          20           25           30
Glu Thr Val Tyr Tyr Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu
          35           40           45
Tyr Thr Ser His Ile Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu
          50           55           60
Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr
65           70           75           80

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Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser
 85 90 95
 Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
 100 105 110
 Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu
 115 120 125
 Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu
 130 135 140
 Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
 145 150 155 160
 Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
 165 170 175
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 180 185 190
 Glu Cys Val Glu Val Gln Gly Glu Ala Gly Gly Gly Gly Ser Gly Gly
 195 200 205
 Gly Gly Ser Gly Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val
 210 215 220
 Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
 225 230 235 240
 Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
 245 250 255
 Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
 260 265 270
 Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
 275 280 285
 Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
 290 295 300
 Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg
 305 310 315 320
 Gly Glu Cys

<210> 61

<211> 201

<212> PRT

<213> Homo sapiens

<400> 61

Asp Glu Val Ala Ile Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser
 1 5 10 15
 Thr Asn Met Lys His Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly
 20 25 30

Glu	Thr	Val	Tyr	Tyr	Ser	Val	Glu	Tyr	Gln	Gly	Glu	Tyr	Glu	Ser	Leu	
35							40		45							
Tyr	Thr	Ser	His	Ile	Trp	Ile	Pro	Ser	Ser	Trp	Cys	Ser	Leu	Thr	Glu	
50							55		60							
Gly	Pro	Glu	Cys	Asp	Val	Thr	Asp	Asp	Ile	Thr	Ala	Thr	Val	Pro	Tyr	
65						70		75							80	
Asn	Leu	Arg	Val	Arg	Ala	Thr	Leu	Gly	Ser	Gln	Thr	Ser	Ala	Trp	Ser	
				85						90		95				
Ile	Leu	Lys	His	Pro	Phe	Asn	Arg	Asn	Ser	Thr	Ile	Leu	Thr	Arg	Pro	
			100						105		110					
Gly	Met	Glu	Ile	Pro	Lys	His	Gly	Phe	His	Leu	Val	Ile	Glu	Leu	Glu	
115						120		125								
Asp	Leu	Gly	Pro	Gln	Phe	Glu	Phe	Leu	Val	Ala	Tyr	Trp	Thr	Arg	Glu	
130						135		140								
Pro	Gly	Ala	Glu	Glu	His	Val	Lys	Met	Val	Arg	Ser	Gly	Gly	Ile	Pro	
145						150		155							160	
Val	His	Leu	Glu	Thr	Met	Glu	Pro	Gly	Ala	Ala	Tyr	Cys	Val	Lys	Ala	
				165						170		175				
Gln	Thr	Phe	Val	Lys	Ala	Ile	Gly	Arg	Tyr	Ser	Ala	Phe	Ser	Gln	Thr	
			180						185		190					
Glu	Cys	Val	Glu	Val	Gln	Gly	Glu	Ala								
195						200										

<210> 62
<211> 559
<212> PRT
<213> Homo sapiens

<400> 62															
Val	Pro	Cys	Val	Ser	Gly	Gly	Leu	Pro	Lys	Pro	Ala	Asn	Ile	Thr	Phe
1				5					10					15	
Leu	Ser	Ile	Asn	Met	Lys	Asn	Val	Leu	Gln	Trp	Thr	Pro	Pro	Glu	Gly
			20					25					30		
Leu	Gln	Gly	Val	Lys	Val	Thr	Tyr	Thr	Val	Gln	Tyr	Phe	Ile	Tyr	Gly
		35					40					45			
Gln	Lys	Lys	Trp	Leu	Asn	Lys	Ser	Glu	Cys	Arg	Asn	Ile	Asn	Arg	Thr
	50					55					60				
Tyr	Cys	Asp	Leu	Ser	Ala	Glu	Thr	Ser	Asp	Tyr	Glu	His	Gln	Tyr	Tyr
65					70					75					80
Ala	Lys	Val	Lys	Ala	Ile	Trp	Gly	Thr	Lys	Cys	Ser	Lys	Trp	Ala	Glu
				85					90					95	
Ser	Gly	Arg	Phe	Tyr	Pro	Phe	Leu	Glu	Thr	Gln	Ile	Gly	Pro	Pro	Glu
			100					105					110		

Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala
 115 120 125
 Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln
 130 135 140
 Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
 145 150 155 160
 Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
 165 170 175
 Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
 180 185 190
 Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala
 195 200 205
 Arg Thr Leu Lys Asp Gln Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 210 215 220
 Gly Gly Gly Gly Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
 225 230 235 240
 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 245 250 255
 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 260 265 270
 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 275 280 285
 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 290 295 300
 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 305 310 315 320
 Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
 325 330 335
 Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val
 340 345 350
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 355 360 365
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
 370 375 380
 Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 385 390 395 400
 Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 405 410 415
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 420 425 430
 Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile
 435 440 445

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 450 455 460
 Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 465 470 475 480
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 485 490 495
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 500 505 510
 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 515 520 525
 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 530 535 540
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 545 550 555

<210> 63
 <211> 214
 <212> PRT
 <213> Homo sapiens

<400> 63
 Val Pro Cys Val Ser Gly Gly Leu Pro Lys Pro Ala Asn Ile Thr Phe
 1 5 10 15
 Leu Ser Ile Asn Met Lys Asn Val Leu Gln Trp Thr Pro Pro Glu Gly
 20 25 30
 Leu Gln Gly Val Lys Val Thr Tyr Thr Val Gln Tyr Phe Ile Tyr Gly
 35 40 45
 Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys Arg Asn Ile Asn Arg Thr
 50 55 60
 Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp Tyr Glu His Gln Tyr Tyr
 65 70 75 80
 Ala Lys Val Lys Ala Ile Trp Gly Thr Lys Cys Ser Lys Trp Ala Glu
 85 90 95
 Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr Gln Ile Gly Pro Pro Glu
 100 105 110
 Val Ala Leu Thr Thr Asp Glu Lys Ser Ile Ser Val Val Leu Thr Ala
 115 120 125
 Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp Leu Pro Val Ser Met Gln
 130 135 140
 Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val Ser Val Leu Asn Thr Lys
 145 150 155 160
 Ser Asn Arg Thr Trp Ser Gln Cys Val Thr Asn His Thr Leu Val Leu
 165 170 175

Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys Val His Val Glu Ser Phe
 180 185 190
 Val Pro Gly Pro Pro Arg Arg Ala Gln Pro Ser Glu Lys Gln Cys Ala
 195 200 205
 Arg Thr Leu Lys Asp Gln
 210

<210> 64
 <211> 19
 <212> PRT
 <213> Homo sapiens

<400> 64
 Glu Glu Ile His Ala Glu Leu Arg Arg Phe Arg Arg Val Pro Cys Val
 1 5 10 15
 Ser Gly Gly

<210> 65
 <211> 207
 <212> PRT
 <213> Homo sapiens

<400> 65
 Leu Pro Lys Pro Ala Asn Ile Thr Phe Leu Ser Ile Asn Met Lys Asn
 1 5 10 15
 Val Leu Gln Trp Thr Pro Pro Glu Gly Leu Gln Gly Val Lys Val Thr
 20 25 30
 Tyr Thr Val Gln Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys
 35 40 45
 Ser Glu Cys Arg Asn Ile Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu
 50 55 60
 Thr Ser Asp Tyr Glu His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp
 65 70 75 80
 Gly Thr Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe
 85 90 95
 Leu Glu Thr Gln Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu
 100 105 110
 Lys Ser Ile Ser Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn
 115 120 125
 Pro Glu Asp Leu Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys
 130 135 140
 Tyr Asn Val Ser Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln
 145 150 155 160

Cys Val Thr Asn His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr
 165 170 175
 Leu Tyr Cys Val His Val Glu Ser Phe Val Pro Gly Pro Pro Arg Arg
 180 185 190
 Ala Gln Pro Ser Glu Lys Gln Cys Ala Arg Thr Leu Lys Asp Gln
 195 200 205

<210> 66

<211> 150

<212> PRT

<213> Homo sapiens

<400> 66

Cys Arg Asn Ile Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr Ser
 1 5 10 15
 Asp Tyr Glu His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly Thr
 20 25 30
 Lys Cys Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu Glu
 35 40 45
 Thr Gln Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys Ser
 50 55 60
 Ile Ser Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro Glu
 65 70 75 80
 Asp Leu Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr Asn
 85 90 95
 Val Ser Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys Val
 100 105 110
 Thr Asn His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu Tyr
 115 120 125
 Cys Val His Val Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala Gln
 130 135 140
 Pro Ser Glu Lys Gln Cys
 145 150

<210> 67

<211> 196

<212> PRT

<213> Homo sapiens

<400> 67

Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met Lys His
 1 5 10 15


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<210> 68
<211> 203
<212> PRT
<213> Homo sapiens
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<400> 68

Asp 1	Glu	Val	Ala	Ile	Leu	Pro	Ala	Pro	Gln	Asn	Leu	Ser	Val	Leu	Ser
				5					10					15	
Thr	Asn	Met	Lys	His	Leu	Leu	Met	Trp	Ser	Pro	Val	Ile	Ala	Pro	Gly
			20					25					30		
Glu	Thr	Val	Tyr	Tyr	Ser	Val	Glu	Tyr	Gln	Gly	Glu	Tyr	Glu	Ser	Leu
		35					40					45			
Tyr	Thr	Ser	His	Ile	Trp	Ile	Pro	Ser	Ser	Trp	Cys	Ser	Leu	Thr	Glu
	50					55					60				
Gly	Pro	Glu	Cys	Asp	Val	Thr	Asp	Asp	Ile	Thr	Ala	Thr	Val	Pro	Tyr
65					70					75				80	
Asn	Leu	Arg	Val	Arg	Ala	Thr	Leu	Gly	Ser	Gln	Thr	Ser	Ala	Trp	Ser
				85					90					95	

Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro
 100 105 110
 Gly Met Glu Ile Pro Lys His Gly Phe His Leu Val Ile Glu Leu Glu
 115 120 125
 Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu
 130 135 140
 Pro Gly Ala Glu Glu His Val Lys Met Val Arg Ser Gly Gly Ile Pro
 145 150 155 160
 Val His Leu Glu Thr Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala
 165 170 175
 Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr
 180 185 190
 Glu Cys Val Glu Val Gln Gly Glu Ala Ile Pro
 195 200

<210> 69

<211> 196

<212> PRT

<213> Homo sapiens

<400> 69

Leu Pro Ala Pro Gln Asn Leu Ser Val Leu Ser Thr Asn Met Lys His
 1 5 10 15
 Leu Leu Met Trp Ser Pro Val Ile Ala Pro Gly Glu Thr Val Tyr Tyr
 20 25 30
 Ser Val Glu Tyr Gln Gly Glu Tyr Glu Ser Leu Tyr Thr Ser His Ile
 35 40 45
 Trp Ile Pro Ser Ser Trp Cys Ser Leu Thr Glu Gly Pro Glu Cys Asp
 50 55 60
 Val Thr Asp Asp Ile Thr Ala Thr Val Pro Tyr Asn Leu Arg Val Arg
 65 70 75 80
 Ala Thr Leu Gly Ser Gln Thr Ser Ala Trp Ser Ile Leu Lys His Pro
 85 90 95
 Phe Asn Arg Asn Ser Thr Ile Leu Thr Arg Pro Gly Met Glu Ile Pro
 100 105 110
 Lys His Gly Phe His Leu Val Ile Glu Leu Glu Asp Leu Gly Pro Gln
 115 120 125
 Phe Glu Phe Leu Val Ala Tyr Trp Thr Arg Glu Pro Gly Ala Glu Glu
 130 135 140
 His Val Lys Met Val Arg Ser Gly Gly Ile Pro Val His Leu Glu Thr
 145 150 155 160
 Met Glu Pro Gly Ala Ala Tyr Cys Val Lys Ala Gln Thr Phe Val Lys
 165 170 175

Ala Ile Gly Arg Tyr Ser Ala Phe Ser Gln Thr Glu Cys Val Glu Val
 180 185 190
 Gln Gly Glu Ala
 195

<210> 70
 <211> 135
 <212> PRT
 <213> Homo sapiens

<400> 70
 Cys Ser Leu Thr Glu Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr
 1 5 10 15
 Ala Thr Val Pro Tyr Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln
 20 25 30
 Thr Ser Ala Trp Ser Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr
 35 40 45
 Ile Leu Thr Arg Pro Gly Met Glu Ile Thr Lys Asp Gly Phe His Leu
 50 55 60
 Val Ile Glu Leu Glu Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala
 65 70 75 80
 Tyr Trp Arg Arg Glu Pro Gly Ala Glu Glu His Val Lys Met Val Arg
 85 90 95
 Ser Gly Gly Ile Pro Val His Leu Glu Thr Met Glu Pro Gly Ala Ala
 100 105 110
 Tyr Cys Val Lys Ala Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser
 115 120 125
 Ala Phe Ser Gln Thr Glu Cys
 130 135

<210> 71
 <211> 135
 <212> PRT
 <213> Homo sapiens

<400> 71
 Cys Ser Leu Thr Glu Gly Pro Glu Cys Asp Val Thr Asp Asp Ile Thr
 1 5 10 15
 Ala Thr Val Pro Tyr Asn Leu Arg Val Arg Ala Thr Leu Gly Ser Gln
 20 25 30
 Thr Ser Ala Trp Ser Ile Leu Lys His Pro Phe Asn Arg Asn Ser Thr
 35 40 45

Ile Leu Thr Arg Pro Gly Met Glu Ile Pro Lys His Gly Phe His Leu
 50 55 60
 Val Ile Glu Leu Glu Asp Leu Gly Pro Gln Phe Glu Phe Leu Val Ala
 65 70 75 80
 Tyr Trp Thr Arg Glu Pro Gly Ala Glu Glu His Val Lys Met Val Arg
 85 90 95
 Ser Gly Gly Ile Pro Val His Leu Glu Thr Met Glu Pro Gly Ala Ala
 100 105 110
 Tyr Cys Val Lys Ala Gln Thr Phe Val Lys Ala Ile Gly Arg Tyr Ser
 115 120 125
 Ala Phe Ser Gln Thr Glu Cys
 130 135

<210> 72

<211> 15

<212> PRT

<213> Homo sapiens

<400> 72

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 1 5 10 15

INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/US 00/35305

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K16/24 C07K16/28 C07K14/54 A61K39/395 C07K19/00
A61P17/06 A61P11/06 //C07K14/715

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 27103 A (ZYMOGENETICS INC) 3 June 1999 (1999-06-03) abstract page 2, line 10-36 page 4, line 13-17 page 5, line 5-17 page 19, line 11-33 page 37, line 11-33 page 41, line 19-24	1,2,7,8
Y	page 43, line 1-26 --- -/-	3-6

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 April 2001

Date of mailing of the international search report

11.05.01

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Montrone, M

INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/US 00/35305

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 03982 A (FLORENCE KIMBERLY A ;HUMAN GENOME SCIENCES INC (US); DUAN ROXANNE) 28 January 1999 (1999-01-28)	1,2
Y	abstract page 2, line 34 -page 3, line 11 page 5, line 11-39 page 6, line 38 -page 7, line 2 page 35, line 7 -page 36, line 39 page 39, line 17 -page 41, line 21 page 45, line 19-31 page 46, line 20-25	3-6
X	US 5 945 511 A (KHO CHOON J ET AL) 31 August 1999 (1999-08-31)	1,2
Y	abstract column 1, line 25-32 column 4, line 14-28 column 5, line 13-40 column 6, line 49-51 column 15, line 66 -column 16, line 28 column 17, line 1-51 column 18, line 18-21	3-6
Y	MCKINNON M ET AL: "STRATEGIES FOR THE DISCOVERY OF CYTOKINE RECEPTOR ANTAGONISTS" DRUG NEWS AND PERSPECTIVES,XX,XX, vol. 9, 1996, pages 389-398, XP000882849 ISSN: 0214-0934 abstract page 391, column 1, paragraph 2 -column 3, paragraph 1; figure 1	1-6
Y	MOHLER K M ET AL: "IMMUNOTHERAPEUTIC POTENTIAL OF SOLUBLE SYTOKINE RECEPTORS IN INFLAMMATORY DISEASE" FASEB JOURNAL,US,FED. OF AMERICAN SOC. FOR EXPERIMENTAL BIOLOGY, BETHESDA, MD, vol. 6, no. 4, 26 February 1992 (1992-02-26), page A1123 XP002015786 ISSN: 0892-6638 abstract	1-6

-/-

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 00/35305

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 00 42189 A (MURPHY MARIANNE ; FLORENCE KIMBERLY (US); HUMAN GENOME SCIENCES INC) 20 July 2000 (2000-07-20) page 3, line 4-17 page 5, line 27 -page 6, line 31 page 7, line 6-36 page 8, line 1-3 page 9, line 8-12 page 30, line 32-37 page 51, line 19 -page 53, line 26 page 55, line 9-14 page 57, line 9,10 page 62, line 23 -page 64, line 30 page 115, line 5 -page 116, line 25 -----	1,2,9,10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/35305

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 to 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/35305

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9927103 A	03-06-1999	AU 1607799 A BR 9814904 A CN 1282372 T EP 1032671 A NO 20002698 A	15-06-1999 03-10-2000 31-01-2001 06-09-2000 20-07-2000
WO 9903982 A	28-01-1999	AU 8404598 A AU 8571198 A EP 1027430 A EP 1012260 A WO 9903990 A	10-02-1999 10-02-1999 16-08-2000 28-06-2000 28-01-1999
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WO 0042189 A	20-07-2000	AU 2965600 A	01-08-2000

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